The New England
Journal of Medicine

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Volume 238 JANUARY 22, 1948 Number 4

MEDICAL AND HOSPITAL CARE OF THE VETERANS IN MASSACHUSETTS*

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BOSTON

THE entitlement of veterans to hospital and outpatient care under laws and regulations administered by the Veterans Administration is a part of any consideration of provisions for and distribution of medical care in Massachusetts, since there are approximately 600,000 veterans of wartime and peacetime service residing within the Commonwealth. All of these, comprising about 14 per cent of the entire population, are potential beneficiaries of these laws and regulations.

These veterans, men and women, who have served in the military forces are entitled, under existing federal laws, to medical care, including hospitalization or outpatient service for the relief of disabilities incurred in military service. There is further provision that, even though the disability was not incurred in the service, they are entitled to hospital care in Government hospitals for any disability requiring such care, regardless of when incurred, provided that they subscribe to a statement that they are unable to pay for the service elsewhere and provided that beds in Government hospitals are available.

Thus, veterans fall into two categories of entitlement to medical care: those with service-connected disabilities, and those with nonservice-connected disabilities. Of the 600,000 veterans in Massachusetts, approximately 79,000 have disabilities adjudged as service connected. It must be appreciated that many of these disabilities, such as amputations and loss of sight and hearing, as well as residua of wounds, are more or less static and permanent and will require little, if any, medical attention. However, pulmonary, cardiac and various other organic diseases, as well as nervous and mental afflictions, will require hospital or outpatient care for an indefinite period.

Of interest to the medical profession, as well as the public at large, is the plan of the federal Government, through the Veterans Administration, to provide for the medical care of veterans in the Commonwealth.

At the present time, in Massachusetts, the Veterans Administration is operating five hospitals, with 4797 beds, 3100 of which are solely for the care of the mentally afflicted, 498 for tuberculosis, and the remainder — about 1200 — for general medical and surgical cases. These hospitals are as follows: West Roxbury (general, 382 beds); Bedford (neuropsychiatric, 1822 beds, including 85 for women); Rutland 496 beds for tuberculosis; Framingham, formerly the United States Army Cushing General Hospital (general, neuropsychiatric and tuberculosis, 1000 beds) — this is one of the seven centers for paraplegic patients, includes 52 beds for women and is one of the Veterans Administration centers for the rehabilitation of aphasic and neurosurgical patients; and Northampton, 1095 beds for mental cases. In addition, the Veterans Administration has access to 250 beds in other Government hospitals, including the United States Naval Hospital at Chelsea and the United States Marine hospitals at Brighton and Vineyard Haven. As of a recent date, a total of 4724 veterans were hospitalized in Veterans Administration and other Government hospitals in the Commonwealth, 2091 of whom were receiving care for service-connected disabilities, and the remainder — more than half, or 2633 cases — for nonservice-connected ailments. Only 155 patients were hospitalized in civil or state hospitals.

The plans for the immediate future for additional hospital construction provide for a 1000-bed general medical and surgical hospital in Boston and a 1000-bed neuropsychiatric hospital near Boston. Upon completion, during 1950–1951, this will provide a total of about 6700 beds in Veterans Administration hospitals in Massachusetts, with the probability that further additional construction will be required before the estimated peak load is reached — between 1965 and 1970.

Outpatient service is an integral part of medical care for veterans. During a recent month, 9008 veterans received one or more physical examinations, and 12,990 were treated on an outpatient basis,

*Part of a symposium on medical care presented at the annual meeting of the Massachusetts Medical Society, Boston, May 20, 1947.

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either in established Veterans Administration clinics or by physicians in the community in which the veterans reside.

The Veterans Administration has established outpatient clinics in Boston, Worcester, Springfield, Lawrence, Lowell and New Bedford, with 46 full-time physicians and 42 part-time physicians employed. In the hospital service in Massachusetts, there are 70 full-time and 108 part-time physicians, including consultants and attendings, 71 residents and 66 young medical officers detailed from the Army and Navy, making a total of 315.

Although outpatient medical service to entitled veterans is practically restricted to state lines, no such limitation applies to hospital service. In other words, Massachusetts veterans receive outpatient treatment at clinics operated by the Veterans Administration or by civilian clinics or private physicians within the Commonwealth, but the Veterans Administration hospitals serve a veteran population in a general area. For instance, no construction of hospitals for the mentally afflicted or the tuberculous in Rhode Island, New Hampshire or Vermont is contemplated; consequently, beds in the neuropsychiatric hospitals in Massachusetts — at Bedford, Northampton and the proposed new center near Boston — will be available for the care of mentally afflicted veterans from other states.

Regarding the so-called "home-town care of veterans" an unfortunate situation arose, because of misleading publicity that appeared in press releases when this plan was started in certain states, as in Kansas, Michigan and New Jersey. It led many physicians, as well as the veterans themselves, to believe that family physicians could provide any sort of medical treatment, at Government expense. The releases did not stress the fact that the Veterans Administration could pay only for the treatment of service-connected disabilities and that, except in emergencies, the veterans should obtain prior authorization for the service required. Furthermore, it was not made clear that the Veterans Administration must use its established clinics to full capacity, and that veterans may be referred to private physicians only when reporting to the Veterans Administration clinic would work a hardship, such as loss of employment, or because of conditions prohibiting travel. The implementation of this plan in many sections, and this has been applicable to New England, has presented many difficulties, including agreement between the Veterans Administration and the state medical societies concerning a satisfactory fee schedule and the method of carrying the overhead — that is, whether or not an intermediary, such as the Blue Shield or Blue Cross, would serve as such an agent.

Negotiations between the Veterans Administration and officials of the Massachusetts Medical Society, through the Massachusetts Medical Services, Inc., have resulted in the adoption of a reasonably satisfactory schedule of fees for various medical services. It was agreed that the Massachusetts Medical Service, Inc., would serve as the intermediary at a nominal charge for overhead, to be paid by the Veterans Association. Under this plan, the Massachusetts Medical Service, Inc., would receive initial authorization for the examination or treatment of a veteran, or a group of veterans, in a given community. The Massachusetts Medical Service would then advise the veteran, furnishing him with a list of physicians in his community who had expressed willingness to participate and serve. The veteran would go to the physician of his choice, who would submit his bill to the Massachusetts Medical Service for payment.

Authorization for treatment would carry authorization to prescribe indicated medication. The prescription would be presented to a local pharmacy for filling.

However, after the consummation of a contract with the Massachusetts Medical Service, Inc., it was found that the enabling act did not permit its negotiation with a federal agency, and amendatory legislation was requested. Such legislation has not to date been enacted, owing to objections on the part of certain groups.

Accordingly, unless favorable legislation is forthcoming, the implementation of this "home-town care plan" through the services of an intermediary, such as the Blue Shield or Blue Cross, will be impossible, and it will have to be worked out in accordance with the Kansas Plan, which comprehends direct action between the Veterans Administration and each individual physician who may be authorized to examine or treat a veteran.*

There is, of course, no sound objection to this procedure, except that there will be a certain delay in effecting payments to physicians, owing to the paper work required in expending appropriated funds, under rather complicated procedures of Government accounting. With an intermediary functioning and willing to assume responsibility for direct payment to participating physicians, payment would be received more expeditiously.

Over the years, since World War I, the question has repeatedly been raised how far the federal Government should go in furnishing medical and hospital care to those who have served in the military forces. There has never been any question of the Government's obligation to those who became disabled as a direct result of their service, and I assume that no serious objection can be raised to governmental provision for the care of the mentally afflicted and tuberculous, regardless of the time of incurrence of the disability.

After World War I and until 1924, the statutes governing veterans' relief provided only for compensation and medical care for disabilities actually

*Since this paper was delivered the Massachusetts Medical Society has entered into a new agreement with the Veterans Administration providing for the delivery of medical service according to the Kansas Plan.

incurred in service. If those statutes were in effect at this time, the Veterans Administration would be obligated to provide hospitalization for about 35,000 veterans instead of 104,000, the number hospitalized at the end of a recent month, and in Massachusetts, 2090 instead of 4724.

The service-connected cases hospitalized at that time comprised 6800 general medical and surgical, 6000 for tuberculosis and 22,000 classed as neuropsychiatric, the majority of which were psychotic patients. Of the nonservice-connected group under hospital care, about 68,000 in all, 32,000 were classed as general medical and surgical cases, 5800 as tuberculosis, and 31,000 as neuropsychiatric. These are national figures, but practically the same ratios prevail in the several areas throughout the country. Projected into the future, until 1965, when the peak load will be reached, a bed requirement of 225,600, including 7500 for tuberculosis, 121,200 for neuropsychiatric cases and 96,900 for general medical and surgical cases, is estimated. Of this total, probably not more than 35 per cent of the beds will be occupied by veterans with service-connected disabilities.

In the time allotted, I have been able only to touch upon the high points of a federal medical service that provides for a potential load of approximately 14 per cent of the population of the Commonwealth. Although the hospital service is available, under certain legal and regulatory restrictions, to the entire group, it must be recognized that outpatient care in regularly established Veterans Administration clinics or through private physicians is limited to service-connected disabilities, under existing laws. With the lapse of time, when the number of service-connected disabilities becomes more or less static, the requirement for outpatient care will show a downward trend. On the other hand, with the liberal provisions for hospital care, the demand for such care on the part of veterans will increase through the years. In anticipation of this increased demand, the Veterans Administration has estimated a requirement for 15,000 beds for veteran care in New England by 1965.

The possibility of further amendments of the laws to provide outpatient care for veterans for nonservice-connected disabilities cannot be ignored. Continually over the years, since World War I, bilis have been introduced before the Congress on this subject. To date, none have been enacted, but the trend is unquestionably in that direction. Such an amendment would have considerable bearing on the distribution of medical care in the Commonwealth and would most certainly require a much wider utilization of physicians on a part-time or fee basis than under existing procedure.

SURGICAL ASPECTS OF BRONCHIECTASIS*

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IT IS generally agreed that the definitive treatment of bronchiectasis is surgical and that most patients should be considered for lobectomy or pneumonectomy, although many may, after evaluation, be denied operation for a variety of reasons.

In 1941 Riggins[1] wrote: "The morbidity and mortality of untreated and medically treated bronchiectasis is such that the physician who routinely advises young adults with operable bronchiectasis against surgery, is assuming a large responsibility and in all probability renders his patient a great disservice." Corroboration of this statement is obtained in several recent studies, one of the best of which is presented by Perry and King,[2] who, on the basis of follow-up examination of 400 patients, conclude that in twelve years the mortality in the nonsurgically treated cases was 26 per cent, 41 per cent of the patients dying within five years of onset and 15 per cent living twenty years or longer after onset. In the fatal cases, 78 per cent of patients died directly of the disease. Some statistical evidence supports the view that patients who develop bronchiectasis before the age of ten do not live beyond the age of forty. Thus, of persons with the onset in the first decade, only 9 per cent were living at the age of forty or over, whereas the onset was in the first decade in only 15 per cent of the 59 patients who reached the age of forty or over. The operative mortality in 122 lobectomies of the modern type, performed by Churchill at the Massachusetts General Hospital on 116 patients, was 3 per cent. The working and living capacity of the living patients who could be traced was considered excellent in 67 per cent of the surgical group and in 38 per cent of the nonsurgical group. These authors find nonsurgical treatment to be only palliative and believe that, because of the steadily decreasing operative mortality, simple lobectomy may be advised without hesitation. Even with bilateral disease the risk in bilateral lobectomy — of course in two or more stages — is often not too great.

*Part of a symposium on bronchiectasis presented at the annual meeting of the Massachusetts Medical Society, Boston, May 21, 1947.

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Bradshaw, Putney and Clerf[3] studied 242 patients with bronchiectasis. Of these, 112 were living, and 59 had died from bronchiectasis or its complications.

Riggins[1] found the mortality in 85 cases of medically treated bronchiectasis, collected during ten years but with many of the patients observed for only three or four years, to be 14 per cent. It should be added that children stand thoracic operations exceptionally well, and lobectomy early in life is almost certain to obviate the hazards of bronchiectasis that such children must face if they grow to adolescence or adult life with nonsurgical treatment.

Averaging the figures given by various students of the disease, Hinshaw and Schmidt[4] estimate that less than 10 per cent of patients with severe bronchiectasis obtain a satisfactory result from any form of medical treatment, and conclude that the mortality within ten or fifteen years after the diagnosis is made is somewhere between 30 and 50 per cent.

The development of the modern technic of intrahilar dissection and individual ligation[5] has further improved lobectomy as applied to bronchiectasis. Although occasionally it may not prove feasible or may even be impossible in cases of so-called "frozen hilus," because of dense fibrosis resulting from repeated exacerbations of pneumonitis, this technic materially reduces the postoperative complications of empyema and bronchopleural fistula. The advent and increasing availability of penicillin promises a further reduction in the incidence of postoperative empyema. At the Massachusetts Memorial and Boston City hospitals it has been used prophylactically, in many cases both intrapleurally and intramuscularly, as part of the preoperative and postoperative routine, with gratifying results.

Growing knowledge of the surgical anatomy of the detailed structures of the lung, refinements in bronchography and clinical experience have demonstrated that a lobe of the lung is actually made up of a cluster of bronchopulmonary segments. In this connection an important contribution was made by Churchill and Belsey[6] in 1939. They correctly prophesied that the bronchopulmonary segment would replace the lobe as the surgical unit of the lung. Although Nelson[7] had earlier suggested that the lungs are made up of eight lobes — two upper lobes, two middle lobes, the dorsal divisions of the lower lobes and the basal divisions of the lower lobes — it remained for Churchill and Belsey to demonstrate the actual clinical application of this anatomic configuration. They applied the principle of segmental pneumonectomy to resection of the lingula of the left upper lobe ("left middle lobe") by removing the posteromedial segment of the lingula; they also employed the technic in operations on the dorsal divisions of the lower lobes. Such contributions are of value since they point the way to greater conservation of normal pulmonary tissue in cases in which lesions are well localized in a bronchovascular segment of the lung.

Results of Surgery

No discussion of the operative treatment of a disease is complete without reference to the risks involved. Churchill's excellent figures, as reported by Perry and King,[2] were mentioned above. Bradshaw and O'Neill[8] report the results of surgical treatment of bronchiectasis in 76 patients whose disorder was mostly due to an unknown etiologic agent. One death occurred among the 24 patients with disease of the lower lobe and of the lower lobe and lingula — a mortality of 4 per cent. Among 26 patients in whom one lobe was removed but in whom disease was present in other lobes, there were 4 deaths, a mortality of 15 per cent, whereas in 17 patients who had two or more lobes removed there were 3 deaths, a mortality of 18 per cent; 11 of these patients had disease in other lobes. Maier[9] reports 64 cases in which pulmonary resections for bronchiectasis were performed. Lobectomy was done in 55 cases, and pneumonectomy in 9, with 1 operative death — a mortality of less than 2 per cent. Sellors et al.[10] report 100 cases of bronchiectasis operated on by three surgeons employing the individual-ligation technic. Closure of the bronchus was attempted by various means, but no perfect method was found and bronchial fistula of varying size developed in 42 per cent of cases. This is a considerably higher incidence of fistulas than that of most thoracic surgeons in this country. There were 8 deaths, 4 occurring within one month and 4 from four to nineteen months after operation.

Kay and Meade[11] state that pulmonary resection for chronic sepsis with present-day technics, anesthesia and chemotherapy is a safe procedure and can be recommended without hesitation. In 100 cases in which they performed lobectomies, there was only 1 death — an operative mortality of 1 per cent, which compares favorably with that from any other operative procedure.

In a series of 72 patients with unilobar, multilobar, unilateral or bilateral bronchiectasis on whom 93 operations were performed at the Boston City and Massachusetts Memorial hospitals there were 7 operative deaths, a case mortality of 9.7 per cent or an operative mortality* of 7.5 per cent.

An analysis of the deaths reveals that there were 4 deaths occurring within ten days of operation: 1 of surgical shock twelve hours after left-upper-lobe tourniquet lobectomy; 1 of sepsis and open pneumothorax ten days after left-lower-lobe tourniquet lobectomy; 1 of atelectasis and pneumonitis eighty hours after tourniquet lobectomy of the right middle and lower lobes in a bilateral case; and 1 death on the operating table of tension pneumothorax at the conclusion of a right pneumonectomy. Three deaths occurred forty to eighty days after operation: 1 of *Bacillus suipestifer* (*Salmonella*

*"Operative mortality" is defined as the percentage of deaths directly attributable to operation.

choleraesuis) bacteremia forty days after left-lower-lobe tourniquet lobectomy; 1 of nephrosis and chronic empyema eighty days after the completion of bilateral lobectomy; and 1 of massive hemorrhage from a chronic empyema fifty-two days after completion of bilateral dissection of four lobes.

In addition there were 2 deaths from brain abscess eighty-one days and one hundred and twenty-one days respectively after lobectomy in patients who had been discharged from the hospital after the original operation. Both were unilobar cases — 1 a dissection lobectomy, and 1 a tourniquet lobectomy. There was also 1 death from massive hemorrhage eighty days after a tourniquet lobectomy of the right middle and lower portions, the patient having been discharged from the hospital after operation.

Of the 41 unilobar cases, in which the total mortality was 4.8 per cent, tourniquet lobectomy was performed in 12, with 2 deaths (a mortality of 16.6 per cent), and dissection lobectomy in 29, with no deaths.

In the 15 unilateral multilobar cases there were 8 bilobar lobectomies with no deaths, and there were 7 pneumonectomies with 2 deaths, or 28.5 per cent.

A survey of the 16 bilateral cases reveals that 7 were completed with 2 deaths (28.5 per cent); in 9 cases in which only the first side was operated on, 1 patient died (11.1 per cent). The total mortality in these cases was thus 18.7 per cent.

Regarding the extent of the bronchiectasis, which can be accurately determined only by adequate bronchograms, I agree with Alexander,[12] who believes that surgery is the treatment of choice for patients whose lesions are restricted to one lobe, to the right lower and middle lobes, to the left lower lobe and lingula ("left middle lobe") or, in some cases, to all the lobes of one lung (total pneumonectomy), to one lobe of each lung or to two lobes of one lung and one lobe of the other (bilateral lobectomy).

Bilateral lobectomy, in stages, has frequently been performed for bronchiectasis. It is routinely considered when the surgical program of suitable bilateral cases is planned. Churchill[13] reports 6 cases, with 1 death. I have performed bilateral excision in 7 cases, with 2 deaths. As might have been expected, however, and as borne out in Bradshaw and O'Neill's[8] report and the figures cited above, bilateral lobectomy is associated with a considerably higher mortality, since it subjects the patient to two major operations. Moreover, the postoperative period after the first lobectomy is rendered more hazardous because the patient must convalesce with disease remaining in one or more lobes.

Nonsurgical Measures

Although the present safety of pulmonary lobectomy has solved the problem of treatment for approximately half the patients with bronchiectasis, the other half are, for a variety of reasons (particularly because of extensive bilateral lesions), not suitable for the operation. Alexander[12] has discussed nonsurgical methods of treatment that, if properly and faithfully carried out, can effectively alleviate the distressing symptoms of the disease in a large majority of patients.

Postural drainage is the most valuable of the nonsurgical therapeutic measures. Every bronchiectatic patient should have at least one bronchoscopic examination, not only because some undetected important intrabronchial lesion may be discovered but also because the aspiration of secretions and the chemical shrinkage of the bronchial mucosa often bring about improvement in the symptoms.

Penicillin is of no permanent value in the treatment of advanced bronchiectasis, but if the organisms are sensitive it is of considerable benefit in preparing the patient for operation. It frequently decreases the cough and sputum and increases the sense of well-being; occasionally, it changes the character of the sputum. It is also of value in the treatment of the recurrent pneumonic episodes, as well as in decreasing the amount of sepsis and toxicity during the interval stages.

In the average case of bronchiectasis after penicillin is discontinued the symptoms soon recur. Pulmonary resection should not be withheld when indicated because of the false sense of security resulting from temporary benefit.

Complications

Putrid Empyema

Infection of the pleural cavity by a mixed flora is a not infrequent complication of bronchiectasis. The common organisms found are the anaerobic streptococcus and the fusospirochetal group. Acting in symbiosis, they give rise to a pleuritic exudate, which has been variously termed "foul," "stinking" or "putrid" empyema. In many cases actual perforation of an abscess cannot be demonstrated, and it may be assumed that the infection of the pleural cavity results from the rupture of microscopic subpleural abscesses, or perhaps by actual passage of the organisms across the visceral pleura via the subpleural lymphatic vessels, which has been shown to be operative under similar circumstances by several workers.[14, 15]

Whatever the mechanism involved, when the complication of putrid empyema occurs it must be considered, under most circumstances, an acute surgical emergency, in contradistinction to empyemas of ordinary pyogenic origin.[16] This is particularly true when a perforation assumes a valve-like action, and the problem of tension pneumothorax is added to that of the infection. In these cases only prompt decompression by surgical means can avert a catastrophe.

Even if there is no pyopneumothorax, the almost immediate effect of a virulent pleural infection of this type is frequently that of profound peripheral

vascular collapse, which clinically may be indistinguishable from surgical shock. If the diagnosis is suspected, it can be confirmed at once by thoracentesis and the aspiration of putrid, thin pus. When such a finding is made, surgical drainage, amply wide and open, must be undertaken forthwith. Strieder and Lynch[16] have shown that when prompt open drainage is established in putrid empyema, whatever its cause, the mortality drops from the rate of approximately 50 per cent prevailing when less drastic measures are used to about 14 per cent.

Extension of Infection

Extension of the infection, either directly into the contiguous lung parenchyma from bronchiectatic abscesses or by bronchogenic dissemination into the same or a contralateral lung, is a common cause of death in bronchiectasis. In many cases this is due to the inexorable progression of a virulent infection in a host whose tissues offer inadequate resistance. In others, the difficulty stems from the impaired efficiency of the cough mechanism, as a result of which the copious, infected secretions bathing the tracheobronchial tree are not expelled. If a patient is unwilling or unable to cough efficiently because of debility or postoperative pain, frequent intratracheal catheter suction or bronchoscopic aspiration of secretions may suffice to tide him over the critical period until the cough mechanism is again functioning normally. Loss of effective ciliary action by the bronchial mucosa, which normally tends to lift secretions away from the pulmonary periphery, undoubtedly contributes to stagnation of secretions and their gravitation into the alveoli.

It is therefore of the utmost importance, both preoperatively and postoperatively, to employ all the available measures (forced cough, postural drainage, catheter suction and bronchoscopy) to promote evacuation of secretions and to prevent stagnation and gravitation to uninvolved portions of the lung.

Metastatic Brain Abscess

Metastatic brain abscess frequently occurs as a complication of thoracic suppuration; in my own experience it has been uniformly and rapidly fatal. In a recent comprehensive paper, Collis[17] states that only 2 recoveries have been recorded after surgical drainage of brain abscesses secondary to thoracic disease. In his series, this cerebral complication occurred in 4.5 per cent of cases of lung abscess and accounted for 20 per cent of the mortality from lung abscess. There is also some evidence that its incidence has risen with the increase in operative procedures in thoracic suppuration. The experience of Collis is in accord with that discussed above in the over-all mortality for 93 operations for bronchiectasis. Of the total of 10 deaths (7 operative), 2 resulted from brain abscess and occurred eighty-one and one hundred and twenty-one days respectively after operation.

Hemorrhage

Hemorrhage is not an unusual complication of bronchiectasis. When it occurs before operation, as hemoptysis, it is usually mild, but it may at times assume alarming, although rarely fatal, proportions. Frequent hemoptysis is a definite indication for surgery in patients in whom there is, at the same time, no contraindication.

As a postoperative complication of tourniquet lobectomy hemorrhage was a dreaded and, when it occurred, rapidly fatal incident. It resulted from imperfect hemostasis of the lobar or pulmonary pedicle or from latent sepsis with delayed erosion of a large vessel of the pedicle. Fortunately, the modern dissection-ligation technic, whereby the hilar vessels of the lung or lobe are individually treated, has to a large extent obviated this complication.

Summary

The majority of patients with bronchiectasis should be considered for lobectomy or pneumonectomy although many may, after evaluation, be denied operation for a variety of reasons.

The operative results of 93 operations on 72 patients who had bronchiectasis are discussed.

The major complications of bronchiectasis are briefly reviewed.

References

1. Riggins, H. M. Bronchiectasis: morbidity and mortality of medically treated patients. *Am. J. Surg.* 64:50-67, 1941.
2. Perry, K. M. A., and King, D. S. Bronchiectasis: study of prognosis based on follow-up of 400 patients. *Am. Rev. Tuberc.* 41:531-548, 1940.
3. Bradshaw, H. H., Putney, F. J., and Clerf, L. H. Fate of patients with untreated bronchiectasis. *J. A. M. A.* 116:2561-2563, 1941.
4. Hinshaw, H. C., and Schmidt, H. W. Some clinical problems in bronchiectasis. *Dis. of Chest* 10:115-122, 1944.
5. Blades, B., and Kent, E. M. Individual ligation technique for lower lobe lobectomy. *J. Thoracic Surg.* 10:84-101, 1940.
6. Churchill, E. D., and Belsey, R. Segmental pneumonectomy in bronchiectasis: lingula segment of left upper lobe. *Ann. Surg.* 109: 481-499, 1939.
7. Nelson, H. P. Postural drainage of lungs. *Brit. M. J.* 2:251-255, 1934.
8. Bradshaw, H. H., and O'Neill, J. F. Surgical treatment of bronchiectasis: report on 76 patients. *Surg., Gynec. & Obst.* 77:315-318, 1943.
9. Maier, H. C. Surgical treatment of bronchiectasis: factors influencing postoperative morbidity and mortality. *Surgery* 15:789-800, 1944.
10. Sellors, T. H., Thompson, V. C., and Qvist, T. Dissection lobectomy for bronchiectasis: review of 100 cases. *Lancet* 2:101-103, 1944.
11. Kay, E. B., and Meade, R. H., Jr. Penicillin in treatment of chronic infections of lungs and bronchi: analysis of 93 cases. *J. A. M. A.* 129:200-204, 1945.
12. Alexander, J. Roles of medicine and surgery in management of bronchiectasis. *Ann. Int. Med.* 21:565-579, 1944.
13. Churchill, E. D. Symposium on carcinoma of lung: resection of lung. *Surgery* 8:961-991, 1940.
14. Graham, E. A. Influence of respiratory movements on formation of pleural exudates. *J. A. M. A.* 76:784, 1921.
15. Brock, R. C., and Blair, E. A. Importance of respiratory movements in formation and absorption of pleural fluids. *J. Thoracic Surg.* 1:50-73, 1931.
16. Strieder, J. W., and Lynch, J. P. Putrid empyema. *New Eng. J. Med.* 234:1-9, 1946.
17. Collis, J. L. Etiology of cerebral abscess as complication of thoracic disease. *J. Thoracic Surg.* 13:445-470, 1944.

MECHANISMS UNDERLYING PULMONARY AND CARDIAC COMPLICATIONS OF ELECTRICALLY INDUCED CONVULSIONS*

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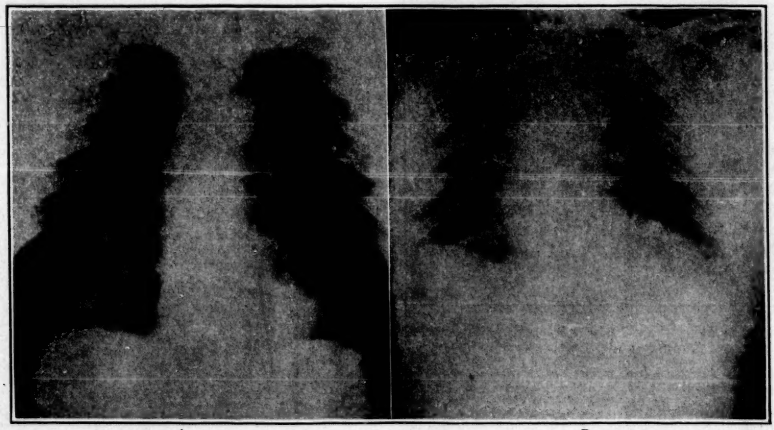
THE changes in pulmonary function observed during electrically induced convulsions account for the development of atelectasis and, more rarely, lung abscess in patients receiving electroshock therapy. A convulsion induced by electric shock is ushered in by maximal forced expiration, which is then maintained throughout the seizure.[1–3] Roentgenograms made at the height of the tonic phase of such seizures uniformly show an extreme degree of elevation of the diaphragm, together with some narrowing of the intercostal spaces; marked compression of the lung results (Fig. 1). With the end of the convulsion the patient relaxes, and the lungs re-expand to approximately their normal size.



A B

FIGURE 1. *Elevation of the Diaphragm during Electrically Induced Convulsions.*

A demonstrates a roentgenogram of the chest immediately before electroshock, and B one at the height of the tonic phase of the seizure, twenty seconds after the start of the convulsion.

During the seizure profuse salivation occurs, apparently as a consequence of autonomic stimulation; in addition it is possible that the marked elevations in blood carbon dioxide tension[3] and blood lactic acid[4] that have been noted stimulate increased secretion of the salivary glands.[5] Roentgenograms made during seizures suggest that bronchial secretion is likewise increased at this time (Fig. 1). Maximal inspiration, such as that occurring at the end of the seizure,[3] causes the aspiration of some of this material into portions of the previously compressed lung, and small bronchi may become occluded; failure of portions of the lung so blocked off to re-expand causes the atelectasis that may be found. It is probable that patchy atelectasis is more common than is usually recognized, for the condition gives rise to no symptoms and clears up in a few days. On the other hand, if infection localizes in an atelectatic area development of an abscess may

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result. This complication is rare, however, having occurred only once in 200 patients given electroshock therapy during the last five years (Fig. 2).

The following case is regarded as typical.

E. W. G., a 65-year-old unmarried typist, entered the hospital voluntarily on October 11, 1946, complaining of agitation and depression of 6 months' duration. A diagnosis of involutional melancholia was made, and physical and laboratory examinations showing no evidence of organic

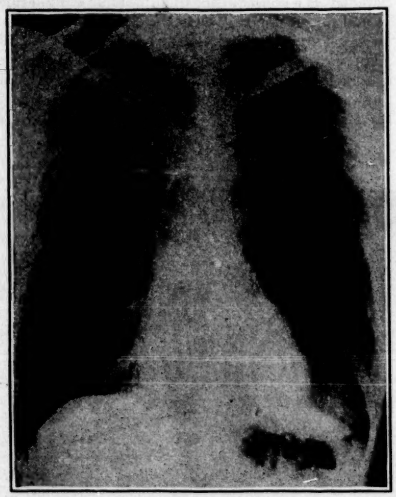

FIGURE 2. *Lung Abscess, Absent before Treatment, Detected after Eighth Shock.*

disease, electroshock therapy was recommended. Because roentgenograms demonstrated an old compression fracture of the spine and deformity of the pelvis apparently consequent to a serious accident 19 years previously, curare (Intocostrin*) was used.

Treatments were begun on October 21 and given 3 times weekly; respiration was not depressed after the treatments. Improvement was rapid, but after the eighth treatment on November 6 the patient was noted to have fever, chilly sensations and a slight cough, and treatments were stopped. The cough was productive of a small amount of foul sputum, which the patient swallowed.

Physical examination was not remarkable except for a temperature of 101°F.; roentgenograms showed an abscess of the lung. On November 14 penicillin in doses of 100,000 units given intramuscularly every 3 hours was started, and 2 days later the temperature was normal. The white-cell count varied between 9800 and 17,000 during the next few weeks. On January 4, 1947, the penicillin dosage was changed to 100,000 units in wax once daily. On January 10 the patient was considered cured clinically and by x-ray study. During the period of the pulmonary infection the depression recurred in a severe form. Another course of electroshock therapy with curare in March and April resulted in clinical cure; no pulmonary complications developed.

*Kindly supplied by E. R. Squibb and Sons, New York City.

The reported exacerbation of latent tuberculous infection may be based on similar mechanisms and also on the tearing of brittle fibrous patches containing tuberculous organisms.

The marked changes in intrathoracic pressure that favor the occurrence of pulmonary lesions serve, on the other hand, to protect the heart during electrically induced seizures. The increase in intrathoracic pressure exerts a force on the outside of the coronary arteries that prevents an increase in difference between the internal and external pressures on the walls of these vessels and may even cause a decrease; brittle coronary arteries are thereby protected from damage. In addition the change from the normal negative intrapleural pressure to a positive pressure during the seizure retards the pas-

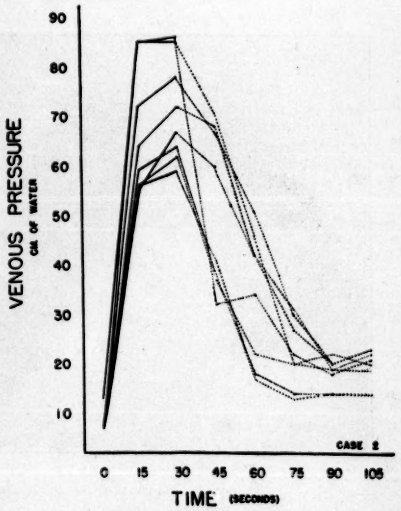

FIGURE 3. *Rise in Peripheral Venous Pressure during Eight Electroshock Treatments.*

The solid line indicates readings during the seizure, and the dotted lines those made after the seizure.

sage of blood from the periphery into the heart; this change is reflected in the increase in peripheral venous pressure noted during electrically induced seizures[2, 6] (Fig. 3). As a consequence of the diminished venous return of blood the heart becomes smaller than normal (Fig. 1), and its work is decreased. Accordingly, it is apparent that the great increase in metabolism that occurs during the thirty or forty seconds of a convulsion is not associated

with a corresponding increase in strain upon the heart at that time. After the end of the convulsion, the cardiac work is increased, judging by the acceleration of circulation time.[7] However, this increase in the work of the heart is related in large part to the discharge of the accumulated oxygen debt, a process that requires many minutes; the cardiac work corresponding to the metabolic increase brought about by the convulsion is therefore not concentrated in the brief period of the seizure but is spread over a longer period and, accordingly, usually does not reach a dangerous level at any one time. Nevertheless, myocardial infarction has been reported to occur in relation to electroshock therapy; the damage probably is done shortly after rather than during the convulsion. Another factor making for a transient increase in cardiac work at this time is the return to the heart of the blood impounded in the periphery during the seizure; this release of blood occurs almost entirely during the first minute after the convulsion, for the venous pressure falls almost to normal during that time (Fig. 2).

In the following case electroshock therapy apparently aggravated the effects of an already present coronary sclerosis.

A. H. L., a 52-year-old executive, became depressed in January, 1945, and because of the marked progression of his symptoms sought psychiatric advice in November of that year. The past history was not contributory except for mild hypertension. On November 1 an electrocardiogram was normal except for left-axis deviation and inverted P and T waves in Lead 3. The patient was given five electroshock treatments without untoward event in November and improved markedly. However, he noted for the first time the development of squeezing precordial exertional discomfort, aggravated by exposure to cold and relieved by rest. Physical examination at that time was not remarkable except for a blood pressure of 168/110. Electrocardiograms in March, 1946, showed left-axis deviation and an inverted T wave in Lead 1. Roentgenograms 3 months later revealed prominence of the left ventricle and hypertrophic changes in the spine. Electrocardiograms at that time disclosed a sinus bradycardia (the rate being 50), left-axis deviation and a low T wave in Lead 1. The two-step stair test, performed in a cold room, caused dyspnea and reproduced the precordial discomfort that the patient had experienced spontaneously during his normal activities. It was concluded that he had developed angina pectoris and changes in the electrocardiogram after electroshock therapy and therefore fell into the small group of patients in whom the effects of coronary sclerosis were aggravated by induced seizures.

The rush of blood from the periphery into the right auricle and great veins of the thorax during the postconvulsive period probably accounts for the cardiac arrhythmias that may occur at that time; the rhythm is normal during at least the last half of the seizure (Fig. 4). The arrhythmias are vagal in type[7–9] and are apparently consequent to reflexes activated by sudden distention of the auricles and great thoracic veins.[8]

It is apparent that diminution of the postconvulsive strain upon the heart would be accomplished by a decrease in the oxygen debt developed and in the amount of blood incarcerated in the periphery during the seizure. This can be effected by the use of a suitable preparation of curare; it is possible to administer electroshock therapy to patients of advanced age and with electrocardiographic evidence of cardiac damage through the use of this drug.[10] It must be borne in mind that a solution of d-tubocurarine is the drug of choice, since Intocostrin may contain impurities that exaggerate to a dangerous degree the vagal impulses that influence cardiac rhythm.[11]

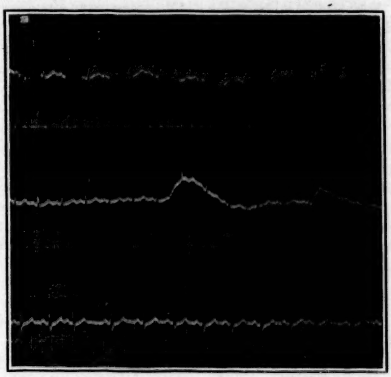

FIGURE 4. *Continuous Strip of Electrocardiogram, Showing Absence of Arrhythmia during the Seizure.*

Normal electrocardographic complexes are interspersed among action currents resulting from clonic muscular contractions.

REFERENCES

1. Cleckley, H. M., Hamilton, W. P., Woodbury, R. A., and Wolpitto, P. Blood pressure studies in patients undergoing convulsive therapy. *South. M. J.* 35:375-381, 1942.
2. Silfverskiöld, B. P., and Amark, C. Disturbance of circulation in convulsions of epileptic type. II. Arterial and venous pressure during electroshock. *Acta med. Scandinav.* 113:191, 1943.
3. Altschule, M. D., Sulzbach, W. M., and Tillotson, K. J. Effects of electrically induced convulsions upon respiration in man. *Am. J. Psychiat.* (in press).
4. Elliott, K. A. C., Rivers, T. D., Elliott, F. H., and Platt, B. Effects of insulin, metrazol, and electric shock on blood pyruvate, lactate, and glucose. *J. Lab. & Clin. Med.* 26:1928-1934, 1941.
5. Brassfield, C. R. Flow and pH change of submaxillary saliva associated with variations in acid-base equilibrium. *Am. J. Physiol.* 144:43-50, 1945.
6. Altschule, M. D., Sulzbach, W. M., and Tillotson, K. J. Changes in peripheral venous pressure during and after electrically induced convulsions in man. *Arch. Neurol. & Psychiat.* (in press).
7. *Idem.* Significance of changes in electrocardiogram after electrically induced convulsions in man. *Arch. Neurol. & Psychiat.* (in press).
8. Bellet, S., Kershbaum, A., and Furst, W. Electrocardiogram during electric shock treatment of mental disorders. *Am. J. M. Sc.* 201: 167-177, 1941.
9. Kline, E. M., and Fetterman, J. L. Electrocardiographic changes following electrically induced convulsions. *Am. Heart J.* 24:665-670, 1942.
10. Altschule, M. D., and Tillotson, K. J. Modification by means of curare of circulatory changes occurring during electrically induced convulsions in man: with note on d-tubocurarine. *Arch. Neurol. & Psychiat.* (in press).
11. *Idem.* Untoward reactions to curare consequent to vagal hyperactivity occurring after electrically induced convulsions in man. *Arch. Neurol. & Psychiat.* (in press).

ANGIOCARDIOGRAPHY: ITS USE IN THE DIAGNOSIS OF PATENT DUCTUS ARTERIOSUS*

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ANGIOCARDIOGRAPHY—contrast visualization of the heart and great vessels—was first made a practical procedure by Robb and Steinberg[1] in 1938. In subsequent reports these authors have described in detail their technic of employing serial roentgenograms after the rapid intravenous injection of 70 per cent Diodrast[2] and, along with many others, have reported their observations in normal and pathologic cardiovascular systems. It is the purpose of this report to review briefly the clinical applications of angiocardiography, to discuss the use of this technic in a rural hospital and to report its use in the diagnosis of a case of patent ductus arteriosus.

CLINICAL APPLICATIONS

Angiocardiography has, in general, two great advantages: it enables one to outline and differentiate the various components of the cardiac and great-vessel silhouettes; and it makes possible the differentiation of vascular and nonvascular mediastinal shadows. This technic has been employed profitably in the more academic study of normal hearts[3] and of various types of acquired cardiovascular disease — rheumatic,[4] arteriosclerotic,[5] hypertensive,[5] syphilitic[5] and pulmonary.[6] Its more practical use has been reported in cases of the superior-vena-cava syndrome,[7] demonstrating the site of an arteriovenous fistula of the subclavian vessels[8] and in differentiating aneurysms of the great vessels from other mediastinal masses.[9] Steinberg,[10] however, has mentioned 2 cases in which the dye did not fill the aneurysms sufficiently for their demonstration.

In congenital cardiovascular lesions, cases have been studied and reported of dextrocardia[11] and intracardiac shunts.[12] The greater value of angiocardiography, however, is in cases of congenital lesions amenable to surgery. By this technic it has been possible to demonstrate definitely the lesions in pulmonic stenosis[13] and coarctation of the aorta.[14] The findings in cases of patent ductus arteriosus are discussed below. Its use has not yet been reported in anomalies of the aortic arch of the type whose surgical treatment has been reported by Gross and Ware,[15] but again the abnormality could be exactly demonstrated. It is true that in typical cases of all four lesions the diagnosis can be made by careful clinical and roentgenographic examination. But the 2 cases of coarctation described by Grishman et al.[14] were atypical ones diagnosed as rheumatic heart disease and hyperthyroidism before the lesions were demonstrated by angiocardiography. In the case of patent ductus reported below, it is believed that the diagnosis could not have been established without angiocardiographic studies. It is also true that in cases of pulmonic stenosis and patent ductus the diagnosis can be made most accurately by cardiac catheterization,[16] but this is an intricate procedure and is not always available. Because of the great benefit of surgery to patients with these four lesions, it seems imperative to employ angiocardiography in atypical or suspected cases, so that no patient may be denied surgery for want of an accurate diagnosis.

In the 27 cases of patent ductus arteriosus studied by Steinberg et al.,[17] a distinct localized dilatation of the aorta was noted in 26. The ductus itself could not be opacified. The authors postulated that this dilatation represented either the infundibulum of the ductus, always known to be funnel shaped at its aortic end, or a traction aneurysm of the descending aorta at the base of the ductus, as originally described by Thoma. In 3 of the 12 cases in which the diagnosis was confirmed by operation, silver clips were placed on top of the ductal ligatures. Repeat angiocardiograms in these cases showed the clips to be in the exact location of the aortic dilatation. In the case in which the aortic lesion was not demonstrable, it seems possible that the clinical diagnosis might be questioned in the absence of a machinery murmur or thrill and in the presence of a peculiar axis deviation by electrocardiogram. A "slight dilatation of the descending portion of the aorta" was noted in only 1 other of the many patients examined by Steinberg et al. This patient was later found at autopsy to have an interventricular septal defect occluded by bacterial vegetations and pulmonic insufficiency secondary to an anomalous posterior pulmonic-valve leaflet (Case 3).[12]

ANGIOCARDIOGRAPHY IN A RURAL HOSPITAL

When this technic was employed for the first time, there were two considerations: the precautions that must be taken to make the procedure safe; and whether the method could be employed with the equipment available.

To determine what precautions should be taken, the American literature on fatalities from the administration of 35 per cent Diodrast was reviewed. Pendergrass et al.,[18] in their extensive review, reported 26 cases, and reports of 10 others are to be found in the literature. Of this entire group,

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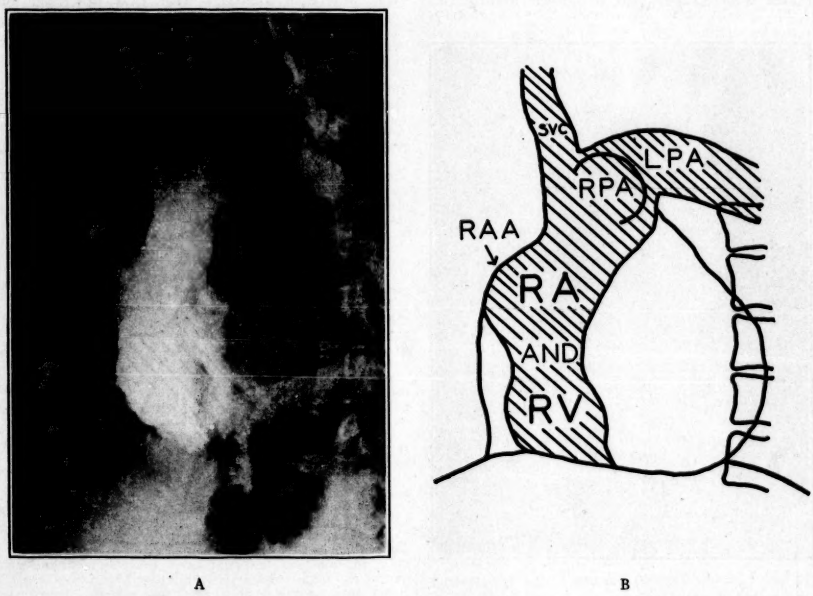
11 can only be mentioned because of insufficient data, and in 10 others Diodrast could not be identified with certainty as the agent responsible for the death. In the remaining 15 cases, death was due to a sudden anaphylactoid or shock-like response in 10[19–21] (Cases 1, 2, 3, 6, 7 and 10),[18] to acute anuria in 2, presumably caused by the effect of Diodrast on previously diseased kidneys that had blocked its rapid excretion (Cases 4 and 19),[18] and to a delayed type of anaphylactoid response in 3 cases, caused in 2 (Cases 9 and 17)[18] by the delayed excretion of Diodrast by previously diseased kidneys.[22]

These deaths due to Diodrast therefore appear to have been caused either by an anaphylactoid response or by the effect of Diodrast on pre-existing renal disease causing delayed excretion or by a combination of the two. To eliminate patients who may have an anaphylactoid response there are two avenues of approach: a careful history of allergy, personal or familial, and sensitivity tests. Although the value of the former appears uncertain at present, it should be taken, and if strongly positive, it seems best not to attempt angiocardiography. If the history of allergy is only slightly positive, studies might be attempted after the prophylactic use of adrenalin[18] or perhaps Benadryl. Also, in view of the cases reported by Dolan[20] and Shanahan,[22] a history of iodide sensitivity should be sought in every case.

Of the sensitivity tests, the best at present appear to be the oral[20] and the ocular.[23] Evidence on the reliability of the skin tests is quite conflicting, but on the basis of Taylor's[3] findings of a lack of correlation between the minor toxic reactions and the intracutaneous test, the test is believed to be of questionable value.

To eliminate patients who would have a delayed Diodrast excretion, the standard phenolsulfonephthalein excretion test is the most satisfactory, because of the similarity of the mode of renal excretion of the drug and Diodrast, both being filtered and secreted. Bishop's[24] standards of an excretion of greater than 15 per cent in fifteen minutes and 30 per cent in one hour were arbitrarily



A B

FIGURE 1. *Angiocardiogram* (A) *and Tracing Made from it* (B), *Taken in the Left Anterior Oblique Position Two and a Half Seconds after the Injection of Diodrast.*

SVC = superior vena cava; RAA = right auricular appendage; RA and RV = right auricle and ventricle; RPA = right pulmonary artery, in cross section; and LPA = left pulmonary artery, in longitudinal section. Note the enlargement of both pulmonary arteries.

accepted. Also adopted was the suggestion, made by the Council of Pharmacy and Chemistry of the American Medical Association when the administration of 70 per cent Diodrast was approved, that the drug be withheld from patients with clinical evidence of hyperthyroidism or hepatic disease.[25]

It was therefore believed that the procedure would be a safe one if each patient fulfilled the following four criteria: a negative history of allergy or iodide sensitivity; negative oral and ocular Diodrast sensitivity tests; a phenolsulfonephthalein excretion of greater than 15 per cent in fifteen minutes and 30 per cent in one hour; and no clinical evidence of hyperthyroidism or hepatic disease.

The technical problems faced were two: the injection of 50 cc. of Diodrast within two seconds and the taking of serial roentgenograms in the ten seconds normally required for the passage of the dye through the heart and great vessels. The first of these was solved by the purchase of a 13-gauge transfusion needle (the only expense) and by manual filing of the bore of a 50-cc. syringe until it was larger than that of the needle. The second was solved by manual passing of the cassettes through the apparatus used for taking stereoscopic films, from which the ejector lever and restraining springs had been removed. An assistant simply pushed a cassette into place after the exposure of the one in the machine, the latter being caught by another assistant as it was ejected. With this method six films were taken in ten seconds with but one practice run. The films were protected before and after exposure by two lead aprons suspended from a cross bar placed over the stereoscopic machine. A small table with two bookends kept the cassettes readily available for the person responsible for placing them in position. The technic employed was otherwise identical with that described by Robb and Steinberg,[3] except that an infusion was kept running through a three-way stopcock, after insertion of the needle, to ensure its patency while the circulation time was determined and positioning films were taken. It should be emphasized that anyone using this technic should be thoroughly familiar with the detailed directions outlined by Robb and Steinberg.

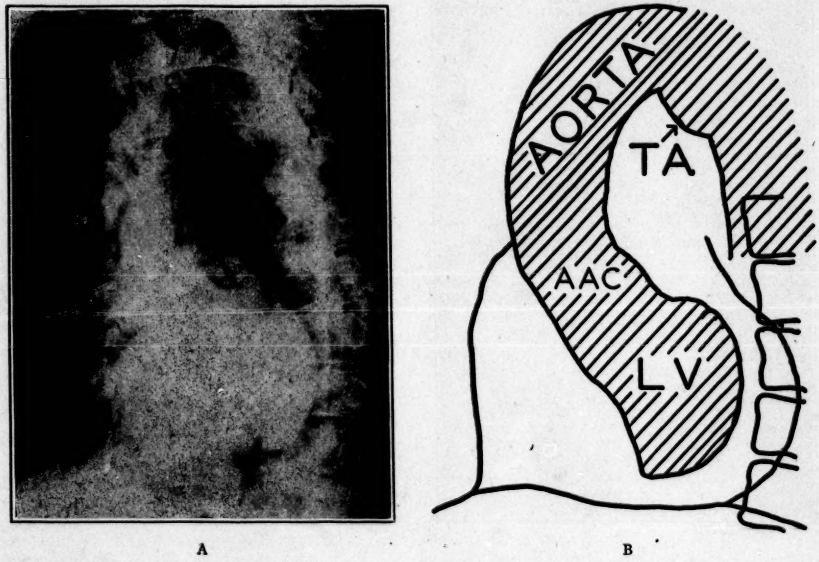


FIGURE 2. *Angiocardiogram* (A) *and Tracing Made from it* (B), *Taken in the Left Anterior Oblique Position Eleven Seconds after the Injection of Diodrast.*
LV = left ventricle; AAC = area of the aortic cusps; and TA = traction aneurysm of the descending aorta.

CASE REPORT*

C. L., a 30-year-old laborer, was first seen at this hospital at the age of 21 for evaluation of "valvular heart trouble." At the age of 9 a "loud heart murmur" had been heard for the first time. During the next 12 years the patient had followed

*This case is reported through the courtesy of Drs. George M. Mackenzie and George H. Humphreys, II.

a vigorous athletic program and did not believe that his exercise tolerance had been less than that of any of the other boys. There was no history of acute rheumatic fever, scarlet fever, tonsillitis, chorea, arthritis, growing pains, precordial pain, edema or cyanosis. Physical examination at that time revealed a well developed and well nourished young man with no evidence of cyanosis, clubbing or edema. The cardiac apex was percussed 11 cm. in the fifth left interspace. No thrill was palpable. There was a regular sinus rhythm. At the base of the heart and in the area between the clavicle and the cardiac border was a continuous murmur with a systolic accentuation. This was heard with diminishing intensity down over the precordium, becoming separate diastolic and systolic murmurs in the third and fourth interspaces along the left border of the sternum. The murmur was transmitted somewhat into the vessels of the neck. There was no evidence of collateral circulation, and strong pulsations were palpable in the legs. Physical examination was otherwise negative. At the time the electrocardiogram was being taken, the murmur was completely absent, returning later in the afternoon as noted above. The electrocardiogram revealed slight slurring of the QRS complexes in all leads and an inverted T wave in Lead 3. There was slight left-axis deviation, but no other abnormalities were noted. A 6-foot film of the heart showed a somewhat rounded left cardiac border, suggesting an enlarged left ventricle. The total transverse measurement of the cardiac shadow was 140 mm., the internal thoracic diameter being 295 mm.

The patient was referred to the hospital because of pyrexia of 6 weeks' duration. During the intervening years he had had no cardiac or respiratory symptoms, was employed at heavy manual labor and was playing semiprofessional baseball. There was no history of recent dental extraction or trauma. Six weeks before admission he had suddenly experienced a shaking chill and had subsequently felt alternately hot and chilly, with a persistent afternoon fever.

The patient appeared ill and had a café-au-lait complexion. There was no cyanosis, clubbing or edema. No precordial shock or thrills were palpable. The left border of the heart was percussed 12.5 cm. in the left fifth interspace. There was a regular sinus rhythm. Along the left border of the sternum at the level of the second and third interspaces was a "whirring, buzzing systolic-diastolic" murmur. Another observer described it as a loud "rough systolic" murmur. There was also a rasping, nontransmitted apical systolic murmur. The spleen was not palpable, and there was no evidence of embolic phenomenon.

The temperature was 103°F., and the blood pressure was 128/66 in the arms and 144/69 in the legs. There was no fall in diastolic pressure after exercise.

A blood culture taken on the day of admission grew colonies of alpha-hemolytic streptococcus in all flasks. The white-cell count was 14,000, with 68 per cent neutrophils. The electrocardiogram was essentially unchanged from the record taken 9 years before. Roentgenographic and fluoroscopic examinations revealed enlargement of the left and right ventricles, with no evidence of enlargement of the left auricle, pulmonary arteries and aorta. There was no hilar dance. The transverse diameter of the heart was 154 mm. Further laboratory studies revealed an ether circulation time of 5.5 seconds, with no Hitzig phenomenon, negative oral and ocular sensitivity tests to Diodrast and a phenolsulfonephthalein excretion of 28 per cent in 15 minutes and 55 per cent in 1 hour.

The patient was hospitalized for 5½ weeks, receiving a total of 56,000,000 units of penicillin. He was afebrile from the 4th day on, with the exception of spikes in temperature to 102°F. on the 12th and 23rd days. All blood cultures taken after the institution of penicillin therapy were negative.

Discussion

During the patient's stay in the hospital the question arose of referring him for surgery, but no definite decision was reached because the diagnosis was not clear cut. Of the ten criteria for the diagnosis of patent ductus listed by Shapiro,[26] this patient definitely had three; four were definitely absent, and three were questionable. He did have an enlarged heart, absence of cyanosis or clubbing and a history of heart disease from early childhood. He did not have a thrill in the pulmonic area, an enlarged pulmonary artery, enlarged and pulsating pulmonary vessels or any stunting of growth. It was questionable if he had a machinery murmur, an increased pulse pressure and a normal electrocardiogram.

In the hope of being able to offer more conclusive evidence of the existence of a patent ductus arteriosus, angiocardiographic studies were performed, with particular attention to the following possibilities: enlargement of the pulmonary arteries, previously not visualized by fluoroscopic examination; and the traction aneurysm of the aorta mentioned above. Prior to examination a normal subject was studied to perfect the technic and to obtain films for comparison.

The angiocardiograms of the patient in the case reported above and tracings made from them are presented in Figures 1 and 2. Both films were taken in the left anterior oblique position. The first, taken two and a half seconds after the start of the injection, shows definite enlargement of both branches of the pulmonary artery. The second film, taken eleven seconds after the start of the injection, reveals a definite fusiform dilatation of the descending aorta, just below the arch and on the side facing the pulmonary arteries. This was also visible in the films taken immediately before and after the one described above. On the basis of these two findings, the diagnosis of patent ductus arteriosus was regarded as confirmed. The patient was referred to Dr. George H. Humphreys, II, who, at operation, found and ligated a patent ductus.

Summary

The clinical applications of angiocardiography are briefly reviewed, with emphasis on its use as a diagnostic aid in atypical cases of congenital cardiovascular lesions amenable to surgery.

The use of this technic in a rural hospital is discussed, the four criteria a patient should fulfill prior to angiocardiographic studies being listed; and the methods by which the difficulties of rapid intravenous injection and rapid serial roentgenograms were overcome being described.

An atypical case of patent ductus arteriosus is reported in which the clinical diagnosis was confirmed by angiocardiographic studies, demonstrating enlargement of the pulmonary arteries and a traction aneurysm of the descending aorta. This diagnosis was confirmed at operation.

I am indebted to Dr. James Drorbaugh and Mr. Ivan Lawrence for assistance in performing these studies.

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References

1. Robb, G. P., and Steinberg, I. Practical method of visualization of chambers of heart, pulmonary circulation, and great blood vessels in man. *J. Clin. Investigation* 17:507, 1938.
2. *Idem.* Visualization of chambers of heart, pulmonary circulation, and great blood vessels in man: practical method. *Am. J. Roentgenol.* 41:1-17, 1939.

3. Taylor, H. K., and McGovern, T. Evaluation of angiocardiography. *J. A. M. A.* **121**:1270-1276, 1943.
4. Grishman, A., Sussman, M. L., and Steinberg, M. F. Angiocardiographic analysis of cardiac configuration in rheumatic mitral disease. *Am. J. Roentgenol.* **51**:33-43, 1944.
5. Robb, G. P., and Steinberg, I. Visualization of chambers of heart, pulmonary circulation, and great blood vessels in heart disease: preliminary observations. *Am. J. Roentgenol.* **42**:14-37, 1939.
6. Sussman, M. L., Steinberg, M. F., and Grishman, A. Contrast visualization of heart and great blood vessels in emphysema. *Am. J. Roentgenol.* **47**:368-376, 1942.
7. Robb, G. P., and Steinberg, I. Visualization of chambers of heart, pulmonary circulation and great vessels: summary of method and results. *J. A. M. A.* **114**:474-480, 1940.
8. Steinberg, M. F., Grishman, A., and Sussman, M. L. Angiocardiographic demonstration of arteriovenous fistula. *Surg., Gynec. & Obst.* **75**:93-96, 1942.
9. Taylor, H. K. Clinical value of angiocardiography. *Dis. of Chest* **11**: 624-638, 1945.
10. Steinberg, M. F. Discussion of Taylor and McGovern.[3]
11. Steinberg, M. F., Grishman, A., and Sussman, M. L. Angiocardiography in congenital heart disease. I. Dextrocardia. *Am. J. Roentgenol.* **48**:141-146, 1942.
12. *Idem.* Angiocardiography in congenital heart disease. II. Intracardiac shunts. *Am. J. Roentgenol.* **49**:766-776, 1943.
13. Grishman, A., Steinberg, M. F., and Sussman, M. L. Tetralogy of Fallot: contrast visualization of heart and great blood vessels. *Radiology* **37**:178-180, 1941.
14. *Idem.* Contrast roentgen visualization of coarctation of aorta. *Am. Heart J.* **21**:364-370, 1941.
15. Gross, R. E., and Ware, P. F. Surgical significance of aortic arch anomalies. *Surg., Gynec. & Obst.* **83**:435-448, 1946.
16. Bing, R. J., Vandam, L. D., and Gray, F. D., Jr. Physiological studies in congenital heart disease. II. Results of preoperative studies in patients with tetralogy of Fallot. *Bull. Johns Hopkins Hosp.* **80**: 121-141, 1947.
17. Steinberg, M. F., Grishman, A., and Sussman, M. L. Angiocardiography in congenital heart disease. III. Patent ductus arteriosus. *Am. J. Roentgenol.* **50**:306-315, 1943.
18. Pendergrass, E. P., Chamberlain, G. W., Godfrey, E. W., and Burdick, E. D. Survey of deaths and unfavorable sequelae following administration of contrast media. *Am. J. Roentgenol.* **48**:741-762 and 793-796, 1942.
19. Goldburgh, H. L., and Baer, S. Death following intravenous administration of diodrast. *J. A. M. A.* **118**:1051, 1942.
20. Dolan, L. P. Allergic death due to intravenous use of diodrast: suggestions for possible prevention. *J. A. M. A.* **114**:138, 1940.
21. Crane, J. J. Sudden death following intravenous administration of diodrast for intravenous urography. *J. Urol.* **42**:745-748, 1939.
22. Shanahan, T. H. Death following use of sodium iodide and diodrast. *New York State J. Med.* **41**:1662, 1941.
23. Archer, V. W., and Harris, I. D. Ocular test for sensitivity to diodrast prior to intravenous urography. *Am. J. Roentgenol.* **48**:763-765, 1942.
24. Bishop, P. A. Discussion of Pendergrass et al.[18]
25. Council on Pharmacy and Chemistry, American Medical Association. Organography with diodrast: concentrated solution: 70 per cent. *J. A. M. A.* **121**:1351, 1943.
26. Shapiro, M. J. Preoperative diagnosis of patent ductus arteriosus. *J. A. M. A.* **126**:934-937, 1944.

ACUTE HEMOLYTIC ANEMIA FROM QUININE USED AS AN ABORTIFACIENT*

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ACUTE hemolytic anemia following the administration of quinine has rarely been observed except in the presence of malaria. Terplan and Javert[1] found 8 cases in the literature and reported a case of their own. All these patients were women who had taken or been given the drug as an abortifacient. All died. They showed evidence of a severe degree of intravascular hemolysis and, in most cases, hemoglobinuria. When measured, the nonprotein nitrogen content of the blood was found to be very high. The intake of the drug was not always beyond usual therapeutic dosage: as little as 0.4 gm. proved fatal in 1 case. Vartan and Discombe[2] have added another fatal case. After the ingestion of 6 gm. of quinine sulfate to induce abortion, the patient quickly developed icterus and black, scanty urine. The terminal blood urea nitrogen was 540 mg. per 100 cc. Hemoglobin casts were found in the kidney at autopsy. The case of a patient who recovered has been reported.[3] She was a twenty-year-old girl who, after taking an unknown amount of quinine to cause abortion, developed jaundice, hemoglobinemia, hemoglobinuria, oliguria and uremia. She recovered after resumption of renal function.

The mechanism of the hemolytic process is not clear. Acute intravascular hemolysis following quinine has been reported apparently only in the presence of malaria or pregnancy. Ponder and Abels[4] found that in rabbits quinine in very large dosage produced a slight fall in red-cell concentration and made the erythrocytes more susceptible to saponin and taurocholate hemolysis. The quantity of quinine necessary was far beyond that which has produced severe hemolytic anemia in man. Perhaps the quinine renders the red cell more susceptible to hemolysins that may be present during malaria and pregnancy. In animal experiments Nocht and Kikuth[5] have shown that very small amounts of quinine may facilitate amboceptor hemolysis.

We have recently observed a similar patient who made a complete recovery from severe intravascular hemolysis following quinine. This case is as follows:

The patient (M. G. H. 526650), a 42-year-old mother of 8 children, entered the hospital on April 14, 1946, because of the sudden appearance of dark-red urine and profuse vaginal bleeding. She described a normal menstrual history. Two weeks before entry, at the time of an expected period, she began to have a spotty vaginal discharge. This continued until 2 days before entry, when she felt chilly and weak and ached all over. On the following morning she was surprised to find that the urine was dark red. She began to have profuse vaginal bleeding and passed many clots. The family noticed that the skin had become slightly yellow. She continued to bleed all day and through the night, and on the morning of admission she passed a piece of tissue accompanied by many blood clots.

The patient had been born near Naples and had come to the United States in 1919. The only history suggestive of malaria was that she had had "Spanish flu" as a girl in Italy during an epidemic. There was no history of familial jaundice, anemia or dark urine either in the patient or in her family, many of whom were available for questioning. She vehemently denied any suspicion of pregnancy or drug ingestion other than that of a few aspirin tablets taken for

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headache on the evening before entry. She had eaten no fava beans. Six pregnancies had been normal. She had had one miscarriage at 6 months following prolonged bleeding, and one threatened miscarriage. One of her children had been born prematurely.

The patient was obese, moderately icteric and acutely ill. She was dyspneic and apprehensive. The liver was slightly tender, and the edge palpable 3 cm. below the costal margin. The spleen could not be felt. There was tenderness over a small area in the left groin. There was a small amount of vaginal bleeding. The uterus was anterior, freely movable and 1½ times the normal size. There was moderate tenderness in both vaults.

The temperature was 102.6°F., the pulse 100, and the respirations 35; the blood pressure was 120/74.

A catheter specimen of urine was wine red and contained 103 mg. of oxyhemoglobin per 100 cc. There were no formed elements in the sediment. There was a +++ test for albumin. The serum of a freshly drawn and centrifuged specimen of blood was the same color as the urine. On analysis several days later it contained 516 mg. of methemoglobin per 100 cc. The red-cell count, which on entry was 4,100,000, fell to 2,800,000 8 hours later. The white-cell count was 50,700, with 86 per cent neutrophils. These showed toxic granulation. The red cells showed great variation in size and shape and moderate spherocytosis. Complete hemolysis of the red cells occurred when they were mixed with 0.55 per cent physiologic saline solution, and partial hemolysis with 0.60 per cent, as compared with normal controls of 0.38 per cent and 0.42 per cent. The osmotic fragility had returned to normal on the 5th hospital day, with complete hemolysis at 0.38 per cent and partial hemolysis at 0.40 per cent. Tests for cold agglutinins, hemolysins and acid hemolysis and a Donath–Landsteiner test done by Dr. Charles P. Emerson, of the Thorndike Memorial Laboratory, were negative. Numerous blood smears for malaria were also negative. A blood Hinton test was negative. Urine obtained on the day of admission contained 1.3 mg. of quinine per liter.

Jaundice disappeared by the 3rd hospital day. The nonprotein nitrogen began to rise on the 2nd hospital day, and by the 5th day had reached a level of 150 mg. per 100 cc., where it remained for 7 days. The carbon dioxide combining power of the blood fell to 18 milliequiv. per liter. Throughout that period the patient complained of headache, vomited frequently and continued to discharge necrotic tissue and blood through the vagina. This tissue proved to be placental in origin. The discharge continued until dilatation and curettage were done on the 17th hospital day. The urine output averaged about a liter per day, and the specific gravity remained close to 1.010. The nonprotein nitrogen slowly fell to normal by the 3rd hospital week. After the curettage the temperature, which had risen to 101°F. daily, returned to normal. In a few days it rose again, and urine cultures, which had previously been sterile, showed a heavy growth of *Escherichia coli*. A 4-day course of streptomycin (1 gm. daily) was followed by relapse. Persistent clearing of the urine and freedom from fever followed a 10-day course. The patient was discharged on the 44th hospital day, when the red-cell count was 4,000,000.

Two weeks after admission she admitted having taken nine large capsules containing a white powder given her by a friend to interrupt a suspected pregnancy.

This report serves to call attention to the fact that quinine is an occasional cause of severe hemolytic anemia associated with jaundice and hemoglobinuria and to emphasize the danger of quinine as an abortifacient.

References

1. Terplan, K. L., and Javert, C. T. Fatal hemoglobinuria with uremia from quinine in early pregnancy. *J. A. M. A.* **106**:529-532, 1936.
2. Vartan, C. K., and Discombe, G. Death from quinine poisoning. *Brit. M. J.* **1**:525, 1940.
3. Wakeman, A. M., Morrell, C. A., Eisenman, A. J., Sprint, D. L. and Peters, J. P. Metabolism and treatment of blackwater fever. *Am. J. Trop. Med.* **12**:407-439, 1932.
4. Ponder, E., and Abels, J. C. Effect of quinine hydrochloride on resistance of rabbit red cells. *Proc. Soc. Exper. Biol. & Med.* **34**: 162-165, 1936.
5. Nocht, B., and Kikuth, W. Über hämolytische Chininwirkungen. *Arch. f. Schiff- u. Tropen-Hyg.* **33**:355-375, 1929.

MEDICAL PROGRESS

SYPHILIS

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Serologic Problems

A diagnosis of syphilis made on purely serologic grounds is to be avoided if possible; nevertheless, the necessity of relying on serologic findings is all too often inescapable. A good example of a typical situation is a survey of 82,070 consecutively examined male maritime enrollees, aged sixteen to fifty-four years.[42] Among this clinically healthy population, there were 783 with positive reactions to the Kahn standard serologic test for syphilis. In 47 per cent of these 783 men a diagnosis of syphilis was eventually made; weakly positive reactions proved to mean syphilis in only 20 per cent of this group, whereas strongly positive reactions indicated syphilis in 80 per cent. Of the 783 original positive reactors, 40 per cent had but a single positive test and were proved not infected. The remaining 13 per cent had nonsyphilitic persistently false-positive reactions. This seems to be an unusually high percentage of persistently false-positive serologic tests for syphilis.

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False-Positive Reactions

Many articles have been written regarding the false-positive reaction, and the list of diseases most commonly producing this phenomenon is well known. Nevertheless, it will again bear repetition. The highest percentage of positive reactions are found in the three syphiloid diseases, yaws, bejel and pinta. Leprosy, malaria, vaccinia and infectious mononucleosis are probably next in order of frequency.

Technical errors are by no means rare. The so-called "biologic false-positive reactions" seem to be found with distressing frequency and are as yet not adequately explained. Many diseases have been reported from time to time as causing occasional false-positive tests for syphilis, including such conditions as upper respiratory infections, virus pneumonia, lymphogranuloma venereum, hyperpyrexia from various causes, serum treatments and assorted immunization procedures. It is also claimed that weak false-positive reactions may be caused by tuberculosis, pregnancy and cancer.[43] If they do occur, the incidence of false-positive reactions from these last three conditions is extremely low. False-positive reactions have also been reported in diseases associated with hyperproteinemia, such as kala-azar.[44] Disorders with associated hyperproteinemia do not necessarily lead to false-positive reactions, however; some may, but there are numerous others that do not. Lupus erythematosus is another disease that apparently must be added to the list. Occasional cases showing false-positive tests for syphilis have been reported from time to time and more frequently in recent years. A recent article describes a group of 3 patients, one of whom came to autopsy; 2 cases of the chronic discoid form of the disease were verified histopathologically, and the third was a case of acute disseminated lupus erythematosus that was examined post mortem.[45] All 3 showed false-positive reactions to syphilis at one or another time during the course of observation.

It seems apparent that nonspecific serologic tests for syphilis, considered uncommon in the past, are now becoming more numerous, particularly in precipitation and flocculation tests such as the Kahn, Kline, Eagle and Mazzini.[46] Moreover, it is suspected that nonspecific positive reactions occur in spinal fluids, and it is suggested that they be considered in early untreated cases in which the cell count, globulin and colloidal gold are normal and only the serologic tests positive. A thoroughly conservative attitude is obviously warranted in the serologic diagnosis of latent syphilis when no history of the disease exists.

There are some circumstances under which a false-positive blood serologic test for syphilis should be particularly suspected. In the complete absence of other evidence of the disease a disagreement in results of complement-fixation and precipitation tests should warrant suspicion, especially if only the precipitation reaction is positive. When quantitative tests are employed and provide fluctuant or low-titer reactions on repetition and if there is a decline toward negativity over a period of several weeks, the patient is probably not infected. If there has been an acute infection of any sort within thirty to sixty days prior to the suspected test, prolonged repetition is warranted, especially if a precipitation reaction alone is used. It is never desirable to depend on a single test under such circumstances; the use of several types of determinations is indicated, as well as the employment of more than one laboratory.

Verification Reactions

A number of "verification" or differential tests have been devised to distinguish between syphilitic and nonsyphilitic reactions. The value of these procedures has not been established, and they are not routinely employed in laboratories for this purpose. They are applicable only to research problems and require a great deal more study before they can be recommended.

Quantitative Reactions

The quantitative determination of reagin titer in a patient's serum is an entirely different procedure and has certain valuable application. Perhaps the greatest value of the quantitative test is in the follow-up study of infants born of syphilitic mothers. There may be a carry-over of the mother's reagin in the child's blood, and a steady drop in reagin titer will indicate that the child itself is not infected; the reverse (when the titer rises or remains persistently elevated) is proof of congenital syphilis. Quantitative tests may be helpful in suspected biologic false-positive reactions; a persistently high reagin titer should indicate syphilis, whereas a slowly dropping titer (without treatment) or fluctuating readings may well mean a biologic false-positive reaction. A third use for the quantitative determination is in the so-called "Wassermann-fast" or seroresistant patients. Quantitative tests may show slow changes that would not otherwise be detectable. An important but strictly experimental application of quantitative serologic tests lies in the evaluation of new antisyphilitic drugs. A most comprehensive study of differential reactions has been carried out at Duke University.[47–52] This work, which is reported in a series of six papers essentially comprising a monograph, represents a tremendous amount of effort. The experiments describe serologic analysis on globulin fractions with the removal of large amounts of serologically inert serum proteins. Syphilitic, presumed biologic false-positive and normal human serums were studied under external conditions in which the reaction, temperature and serum volume were controlled. The fractions thus obtained were subjected to serologic analysis, protein concentration and electrophoretic-component distribution. The known biologic false-positive human serums were seen to show a significant increase in total titer. In both syphilitic and biologic false-positive human serums the reactive antibodies were exclusively associated with serum gamma globulin. It was observed that crude protein fractions of human serums inhibited selectively the serologic activity of the globulin fraction derived from biologic false-positive human serums. The inhibitory factor may be completely

removed by absorption on cholesterol crystals. Inhibition was selectively directed toward the flocculation action of the biologic false-positive type, that of the syphilitic type being hardly affected. The inhibition phenomenon was more specific toward antigens of high chemical purity, such as cardiolipin. It was suggested that inhibition results from competition for the antigen between the antibodies of the biologic false-positive type and the inhibitor. The lack of inhibition of the syphilitic type of reaction is ascribed to a greater affinity of these antibodies for the antigen. These observations suggested a method for the preparation of antigens exclusively specific for syphilis. In mixtures of euglobulin fractions of the syphilitic and biologic false-positive types, inhibition was exclusively directed toward the latter. A preliminary survey analysis with the euglobulin-inhibition method was made on about 2000 human serums of which about 900 were of definitely established diagnostic origin. Somewhat inconclusive results obtained in a small proportion of these serums were ascribed to a combination of limiting factors, and appropriate measures have been suggested to eliminate the resulting ambiguities. Further refinements of the present method were suggested, and a final routine method is being worked out. A general summary given by the authors themselves will perhaps provide the best condensed version of this work:

> The present series of papers describe the evolutionary development of a method for the serologic differentiation between true and biologic false-positive reactions for syphilis. It is based on the inhibitory effect of a heat-stable serum protein component on the serologic activity of euglobulin fractions of biologic false-positive human sera. Agreement between serologic results and diagnostic data was observed in about 95 per cent of the total number of sera of each group.

It is obviously impractical for the practicing physician to indulge in the details of such reports as the foregoing one-hundred-and-twenty-page series of communications. The extremely brief characterization given herein however should serve to portray the tremendous amount of time and effort expended in the laboratory approach to the problem of false-positive serologic tests for syphilis.

An excellent example of the use of quantitative tests for syphilis in evaluating treatment methods is reported from Bellevue Hospital.[53] Four different rapid-treatment programs were employed, and serologic follow-up study was carried out for extensive periods; no patient observed for less than a year was included in the report. It appeared that prolonged low-serologic titers following rapid treatment for early syphilis did not as a rule indicate failure of treatment. In late latent syphilis, sharp rises in post-treatment titers indicated the need for further treatment; so long as a gradual trend downward existed, no further treatment seemed necessary. Among patients with neurosyphilis no correlation was found between the height of the blood reagin titer and the severity of the disease, or between the complement-fixation titers of the blood and spinal fluid.

Cardiolipin Antigen

A distinct refinement in the serodiagnosis of syphilis has been the utilization of cardiolipin antigen in the various serologic tests. This is an essentially chemically pure antigen, which has been found to give more specific results.[54, 55] In nonsyphilitic cases several large series have been studied with apparently more specific results than the antigens routinely used in well established flocculation or precipitation tests. It is also held to be more sensitive than earlier technics. The excellent results obtained with cardiolipin-lecithin antigen and the great simplicity of the technic recommended suggest that a single standard test of the blood for syphilis worthy of universal adoption can be developed. A quantitative macroprecipitation test for syphilis, employing purified cardiolipin-lecithin-cholesterol antigen has also been described.[56] Cardiolipin antigens used in complement-fixation and flocculation tests for syphilis may, however, produce positive reactions with blood from presumably nonsyphilitic donors in cases of malaria, infectious mononucleosis, upper respiratory infections and some supposedly nonsyphilitic patients.[57] Nevertheless, in a health-department laboratory employing several of the so-called "verification reactions" and quantitative serologic tests, the cardiolipin antigen technic is regarded as of the greatest dependability.[58]

An example of the excellence of the cardiolipin antigen is afforded by a study of the incidence of false-positive tests for syphilis in sporozoite-induced vivax malaria.[59] Ninety institutional volunteers for the experiment were found to develop false-positive reactions in 57 cases (63.3 per cent). The blood serums were subjected to a battery of seven serodiagnostic tests for syphilis for periods as long as eighteen months. False-positive reactions appeared on the average eight and a third days after the development of parasitemia. In the majority of subjects, the nonspecific test was transitory and of low degree. Positive reactions resulting from individual attacks of malaria persisted for intervals varying from two to ninety-eight days. Some false-positive tests persisting for longer periods were observed when successive relapses supervened before the seropositivity due to a preceding attack had subsided; a maximum of five hundred and seventeen days was encountered in 1 such case. It was noted that the blood Hinton test and a microflocculation test employing a cardiolipin antigen yielded results of high specificity in this study — a striking fact in view of their recognized high sensitivity in the serodiagnosis of syphilis.

Clinical Problems

By far the largest number of publications on syphilis appearing during the last year have been concerned with therapeutic problems and mainly concern the use of penicillin. It seems advisable therefore to omit the usual subdivisions of this report relating to the clinical phases and treatment of syphilis as separate items, combining them into one main group. Therapy will thus be included with clinical problems and reactions to treatment considered in a separate portion.

Without doubt the greatest single contribution to appear in the literature on syphilis in the past year was a book by Moore.[60] Familiarity with this study seems essential to anyone dealing with syphilis in any of its phases. It should at least be available to the physician who may occasionally encounter this disease. The author has had an unparalleled experience in research, in the study of clinical material, and in directing the largest mass study of syphilis ever undertaken. Participating in the survey were forty-four clinics, including several military installations, numerous United States Public Health Service rapid-treatment centers and many large civilian clinics, mostly university centers. The pharmacology, toxicity and mechanism of action of penicillin are thoroughly covered. The unknown phases of the use of penicillin in syphilotherapy are clearly pointed out, and the difficulties of evaluating this new agent are adequately portrayed. To quote directly, Moore states: "Several more years must elapse before reasonably final statements can be made as to its (penicillin's) use even in early syphilis, to say nothing of the various important late manifestations." Moore believes that in the present state of knowledge the most acceptable method of treatment is through the aqueous solution given intramuscularly every two to four hours, which is definitely a hospital procedure. He discusses in detail the absorption-delaying methods of administering penicillin and indicates that penicillin in oil and beeswax presents the only one that thus far has a limited current practical application. Methods of management of the various stages of syphilis are suggested. Treatment courses are outlined not only for early syphilis but also for the latent disease and late active phases such as hepatic, cardiovascular, ocular, congenital and central-nervous-system syphilis. Moore has most adequately summarized all the currently available data regarding the use of penicillin in syphilis, subjected it to critical analysis and interpreted the information with distinct clarity. It is remarkable that so much has been accomplished within so few years after the introduction of penicillin for the treatment for syphilis. Many more years — at least ten — would normally be required, but the intense co-ordination of effort applied to the study of penicillin in the treatment of syphilis during the war has enabled Moore to take seven-league steps in but a few years' time.

Oral Penicillin

The oral administration of penicillin in the treatment of syphilis should be mentioned only to caution against its use. Experimental work with rabbits and mice infected with syphilis was not encouraging.[61] Limited trials in human subjects have been inconclusive.[62] This mode of administration will be tempting to the general practitioner under many circumstances, but should be strictly prohibited. Little enough is known regarding penicillin by parenteral administration, and oral use can as yet only be condemned.

Penicillin in Early Syphilis

Stokes[63] has placed penicillin at the top of the list of agents for the treatment of syphilis and believes that it will do away with the heavy metals and arsenic altogether. He believes that arsenotherapy has already been replaced by this modality, since penicillin "acts as an arsphenamine," and that there is still a place for bismuth in the treatment of syphilis but thinks that it may eventually also be displaced. The aqueous solution of penicillin administered under hospitalization at intervals of two or three hours is advocated as the procedure of first choice. Suggested total dosages are 2,400,000 to 6,000,000 units for early syphilis, the maximum amount being used for the secondary stages of the disease. For relapsing early infections Stokes advocates double penicillin dosage given at two-hour intervals. He emphasizes the use of adequate quantities of penicillin for a sufficiently long period as initial therapy rather than the repetition of courses of penicillin.

There is available a report of a study of 8000 patients with early syphilis treated by eleven different treatment schedules at sixteen rapid-treatment centers.[64] The treatment programs employed penicillin in total dosages as small as 300,000 units and upwards to 2,400,000 units alone or combined with arsenoxide or bismuth, or both, with various individual doses and treatment periods, or with arsenoxide alone, or combined with bismuth. The five-day arsenical intravenous-drip method gave the most satisfactory results but was abandoned because of the high reaction rate. Penicillin alone was not satisfactory in doses of less than 2,400,000 units. Smaller amounts of penicillin, however, when combined with arsenoxide and bismuth, gave distinctly higher percentages of satisfactory results. A number of other reports indicate that the dose of 2,400,000 units of penicillin may not be sufficient for early syphilis, certainly in the secondary stage.[63, 65–67] Drastically higher total dosage is advocated in revised treatment schedules for the Army.[68] The tentative dosage for early syphilis was stated to be 6,000,000 to 8,000,000 units in seven and a half days. For relapses or reinfections the maximum amount of penicillin is to be administered with the addition of Mapharsen and bismuth. The Veterans

Administration schedule for the management of syphilis is very much like that of the Army, and it also provides a careful classification of all phases of syphilis with treatment schedules for each stage.[69] This is a satisfactory and practical outline, which could well be followed by anyone treating the disease. The combined use of penicillin with arsenoxide and bismuth is properly described, as well as schedules of post-treatment observation. The management of relapses is adequately covered.

Examples of the untoward results of insufficient therapy and a timely warning regarding various pitfalls that may be encountered in the penicillin therapy of syphilis appeared in these columns some months ago.[70] Particularly timely was the advice regarding the ill advised marriage of patients who have been treated for early syphilis with penicillin, especially those who received their therapy during the earlier days of the use of this drug, when lower dosages were employed.

A study of relapse occurring during or after penicillin therapy for syphilis is decidedly enlightening. Among 730 cases of early syphilis treated with varying dosages of penicillin, 110 relapses were observed, some occurring as late as the sixteenth month after cessation of treatment.[71] Second relapses occurring after retreatment with larger doses were usually seen to occur later than first relapses. Some of the original dosage schedules were soon found inadequate and omitted. In each case relapses were treated with double the original dosage, and for second relapses a total quantity as high as 9,000,000 units was administered. The gradually increasing penicillin totals quoted in the last few references indicate clearly the continued need for study of the problem of treating syphilis with penicillin. It is obvious that the optimum dosage schedules are even yet not determined for early syphilis, in which the overwhelming bulk of study has been concentrated. It should also be clear that still more careful follow-up study must be obtained in penicillin treated patients. Monthly titrated serologic tests for a period of at least a year after complete reversal to a negative test would be a desirable attainment. This is often not possible in private practice, but the physician can at least prevail upon the office patient with early syphilis to return at monthly intervals for prolonged observation with routine serologic and physical examination after penicillin therapy.

Words of caution regarding the possibility of masking early infectious syphilis with the penicillin treatment of gonorrhea continue to appear.[71–73] These warnings are deserving of emphasis. The quick cure of gonorrhea with this drug is indeed a blessing, but patients so treated should certainly be followed for periods of not less than six months to be sure that the delayed development of early syphilis will not go unobserved.

Latent Syphilis

Less attention has been directed to this phase of the disease than any other, especially regarding penicillin therapy. Small groups of patients have been observed after penicillin treatment in varying dosage schedules. In general the response has been at least as satisfactory as that with older methods entailing routine chemotherapy. Some workers still advocate the use of iodides and bismuth or bismuth and arsenoxide. Others recommend a penicillin-arsenoxide-bismuth combination.[68, 74] It may be borne in mind that patients in this phase of syphilis do not require anything like the intensive therapy that is necessary for early syphilis or the late and actively destructive forms of the disease. Nevertheless, caution is indicated to avoid a therapeutic paradox; a few injections of bismuth prior to penicillin treatment will prevent a Herxheimer reaction.

Late Syphilis

One of the less common varieties of visceral syphilis is involvement of the pulmonary structures. Syphilis of the lung is most difficult to diagnose and may not even be detected at autopsy. A report on 4 cases has appeared, with a classification and summary of clinical diagnostic criteria.[75] The disease may occur as acute syphilitic bronchial pneumonia, chronic interstitial syphilitic pneumonia, ulcerative and sclerogummatous lesions and syphilitic bronchiectasis. Roentgenographic examination is said to be the most important factor in the detection of pulmonary syphilis and in the determination of the effect of therapy. The x-ray appearance during the response to treatment is the only means by which pulmonary syphilis can be confirmed during the life of the patient.

Cardiovascular syphilis has received considerably more emphasis. In a study of untreated syphilis in the male Negro it was found that definite cardiovascular abnormality was present in about 40 per cent of subjects in the age group over sixty-five years as compared with about 10 per cent of a control series.[76] The treatment of cardiovascular syphilis with penicillin was approached cautiously after untoward reactions had been observed in the earlier experience with this drug. Subsequent studies indicate that significant reactions from penicillin are uncommon in cardiovascular syphilis.[77] In uncomplicated aortitis, doses of penicillin comparable to those used in other phases of late syphilis have been recommended.[74] It seems advisable nevertheless to administer bismuth therapy in preparation for penicillin in all forms of cardiovascular syphilis. In the more serious types of lesions, such as aortic regurgitation and aneurysm, it is questionable whether penicillin should be introduced.

In connection with cardiovascular syphilis, the possibility that malarial therapy used for neuro-

syphilis will produce untoward effects on the heart may be considered. A series of several thousand patients with malaria observed by a competent cardiologist during the recent war did not reveal any cardiac condition that could be specifically attributed to malaria.[78] Any chronic disease, especially one resulting in anemia, may produce tachycardia, premature systoles or a functional systolic murmur, and malaria is no exception. In 50 patients of this large group, who had recurrent malaria and all of whom were studied electrocardiographically, there was no finding that could be considered outside the range of normal variation or of specific import. There were no deaths from acute cardiac disease and no proved cases of chronic cardiac disease in this series, and one would thus expect none from therapy with inoculation malaria.

The treatment of gummatous hepatic syphilis with penicillin has been reported with dramatic alleviation of acute symptoms as well as objective and subjective improvement over an observation period of one and a half to two years.[79]

Syphilitic Nephrosis

A group of 12 cases (0.3 per cent) of renal involvement were found among a large number of patients with secondary syphilis in a period of five years.[80] Ten were classified as nephrosis, and 2 as nephritis. Syphilitic nephrosis is characterized by pronounced albuminuria and cylindruria, with renal-function tests not significantly abnormal. In early syphilitic nephritis there is less albuminuria and more hematuria. The differential diagnosis between syphilitic and nonsyphilitic nephritis may be difficult and can be based only on response to antisyphilitic therapy. All the 12 cases responded satisfactorily to therapy, which consisted of oxophenarsine hydrochloride, oxophenarsine and fever and penicillin alone. Only 1 patient had a Herxheimer reaction. It was suggested that if markedly hemorrhagic nephritis is present, a small initial dosage should be used to avoid a Herxheimer reaction. Syphilitic nephritis should be approached with considerably more caution than the nephrotic disease.

Penicillin in Oil and Beeswax

The disadvantage of penicillin therapy has been the impracticability of three-hourly injections around the clock for all except hospitalized cases. It is obvious that the country as a whole or any one section of it contains insufficient hospital facilities for proper three-hourly administration of rapidly absorbable penicillin solutions. Many attempts have been made to devise means of delaying absorption or excretion of injected penicillin to maintain effective levels in the blood. Of the numerous combinations tested, the most practical is that of calcium penicillin in beeswax and peanut oil, devised by Romansky.[81] The standard preparation maintained therapeutic levels for approximately twenty-four hours after a single injection containing 300,000 units of amorphous calcium penicillin (in 4.8 per cent beeswax by weight in peanut oil) per cubic centimeter of the emulsion. This mixture is commonly referred to as "POB." The originator of POB has reported clinical observation of 4000 cases of assorted infections treated with this substance, among which 600 were more carefully studied.[82] The results were as satisfactory as those obtained by the multiple injections of penicillin in aqueous solution. The incidence of allergic reactions after intramuscular injection of POB was approximately 5 per cent. The preparation has shown no loss of potency at room temperature for a year's time. There is usually some soreness to pressure at the site of injection but usually no more than that following the use of aqueous penicillin. The formation of sterile foreign-body abscesses has occurred most infrequently. So far, there has been no evidence of the development of paraffinomas. Among the 600 cases studied in this report were 75 cases of early syphilis, which comprised the subject of a separate report.[83] The patients received 2,400,000 units during a period of eight days. Follow-up studies of penicillin blood levels showed penicillin present in the blood for a total period of fourteen days. Lesions became darkfield negative in ten to thirty-six hours; both primary and secondary lesions were healed in three to twelve days. Among 60 cases followed for a sufficient time for proper observation, there were only 2 failures. Subsequent work was undertaken with larger doses of penicillin, and a separate group of patients is being studied with the use of a crystalline penicillin suspended in oil and beeswax.

Moore's[60] text does not give unqualified approval of the use of POB but intimates that its usefulness may prove more satisfactory as time passes. In another communication he sounds more optimistic.[84] In any phase of syphilis Moore advises that the average daily adult dose should be 2 cc. (600,000 units), to be given for eight to fifteen days or longer depending on the stage of the infection. For early syphilis a minimum total dose of 4,800,000 to 6,800,000 units of POB is recommended. Other observers have reported a series of 802 patients treated with 4,800,000 units of POB in eight days.[85] An alternate schedule of 300,000 units given twice daily showed no advantage (in percentage of failures or relapses) when compared to the 600,000 units administered in one dose. It was suggested that smaller daily doses if continued for more than eight days might prove more effective. These 802 cases were all early infectious syphilis, and the results were eminently satisfactory; the percentages of failures in the various types of early syphilis were apparently no higher than those in any other type of rapid treatment, including follow-up studies of the cerebrospinal fluid.

A number of variants and improvements on the original POB formula have appeared. There is one

clinical report of the treatment of a small group of patients with various infections with one of these newer preparations that seems entirely satisfactory.[86] Combinations of POB with arsenical and bismuth therapy have also been recommended. In general, the results seem to agree with those obtained by the injection of aqueous injections of penicillin, either alone or in combination with chemotherapy.[87] In the management of syphilis these schedules of ambulatory treatment have a tremendous advantage over the hospitalization requirement entailed by aqueous solution. The co-operation of patients is distinctly better when shorter schedules of seven to ten days are employed. This may not be entirely desirable, since there is still considerable work to be done in establishing the optimal time-dosage relation. These ambulatory schedules will be of the greatest value to practicing physicians, and doubtless many different combinations have been improvised by various persons. When such procedures become standardized and well known, the individual physician will be able to proceed with more confidence in the management of syphilis in office practice. There is one report of the POB treatment of a case of syphilitic nephrosis with a dramatic response.[88]

Chemotherapy

Reports are still appearing upon the short intensive courses of arsenobismuth therapy that were under investigation at the time penicillin appeared.[89, 90] Large groups of patients were studied, especially at military installations. Intensive therapeutic programs were as short as twenty days in some cases. In general the shorter and more intensive programs were found to be inherently toxic, even under expert medical supervision. In spite of relatively good response, both clinically and serologically, these reactions occurred with such severity as to make the intensive programs unjustifiable in comparison to penicillin or penicillin in addition to chemotherapy. When longer schedules were used (twenty-six weeks), the treatment was in general better tolerated, with fewer reactions and generally satisfactory results. It is obvious that great strides had been made in the improvement of older standard chemotherapy routines. The advent of penicillin has of course changed all this, but combinations of penicillin and chemotherapy, as pointed out above, give even more promise.

Newer drugs are still being studied in the field of chemotherapy.[91] Dichlorphenarsine hydrochloride is one that appears to be eminently satisfactory. It has rapid spirocheticidal action and promotes prompt healing of lesions. There is favorable serologic reversal, and reactions for the most part are mild and infrequent. This drug gives promise of being less toxic than arsenoxide products and certainly might be employed with caution as a substitute arsenical for patients exhibiting mild reactions to other drugs of this group, or in combination with penicillin.

(To be concluded)

References

42. Wolman, I. J. Positive reactions to Kahn test for syphilis — their incidence and meaning in healthy American men: survey of 82,070 U. S. Maritime Service enrollees. *Am. J. M. Sc.* **212**:280-288, 1946.
43. Mazzini, L. Y. Serologic trends and aspects. *J. Indiana M. A.* **39**: 282-284, 1946.
44. Blum, L. L. Some diagnostic and serologic problems in present-day management of syphilis. *J. Indiana M. A.* **39**:277-281, 1946.
45. White, C. J. Problem of positive serologic tests for syphilis in lupus erythematosus. *Am. J. Syph., Gonor. & Ven. Dis.* **31**:235-238, 1947.
46. Shaffer, L. W. Nonspecific serologic tests for syphilis. *Am. J. Syph., Gonor. & Ven. Dis.* **31**:221-224, 1947.
47. Neurath, H., et al. Biologic false positive reactions in serologic tests for syphilis. I. Preparation and properties of serologically active serum globulin fractions obtained by fractional precipitation with ammonium sulfate. *Am. J. Syph., Gonor. & Ven. Dis.* **31**:347-373, 1947.
48. Erickson, J. O., Volkin, E., Craig, H. W., Cooper, G. R., and Neurath, H. Biologic false positive reactions in serologic tests for syphilis. II. Preparation and properties of serologically active serum euglobulin fractions obtained by isoelectric precipitation. *Am. J. Syph., Gonor. & Ven. Dis.* **31**:374-396, 1947.
49. Volkin, E., Neurath, H., Erickson, J. O., and Craig, H. W. Biologic false positive reactions in serologic tests for syphilis. III. Preparation and properties of serum protein fractions which inhibit biologic false positive reactions. *Am. J. Syph., Gonor. & Ven. Dis.* **31**:397-412, 1947.
50. Volkin, E., Neurath, H., and Craig, H. W. Biologic false positive reactions in serologic tests for syphilis. IV. Quantitative aspects of inhibition phenomenon. *Am. J. Syph., Gonor. & Ven. Dis.* **31**: 413-435, 1947.
51. Neurath, H., Volkin, E., Craig, H. W., and Erickson, J. O. Biologic false positive reactions in serologic tests for syphilis. V. Preliminary survey analysis with euglobulin-inhibition method for serologic differentiation between true and biologic false positive reactions. *Am. J. Syph., Gonor. & Ven. Dis.* **31**:436-456, 1947.
52. Putnam, F. W., Volkin, E., Craig, H. W., and Neurath, H. Biologic false positive reactions in serologic tests for syphilis. VI. Partial purification of antibodies of syphilitic human sera by adsorption on freshly precipitated calcium phosphate. *Am. J. Syph., Gonor. & Ven. Dis.* **31**:457-468, 1947.
53. Thomas, E. W. Clinical significance of quantitative serologic tests for syphilis. *Am. J. Syph., Gonor. & Ven. Dis.* **30**:317-329, 1946.
54. Kline, B. S. Cardiolipin antigen in microscopic slide precipitation test for syphilis. *Am. J. Clin. Path.* **16**:68-80, 1946.
55. *Idem.* Cardiolipin-lecithin antigen: recent development toward single standard test of blood for syphilis. *Arch. Dermat. & Syph.* **55**: 514-524, 1947.
56. Brown, R. Quantitative macroprecipitation test for syphilis with cardiolipin-lecithin-cholesterol antigen. *Am. J. Syph., Gonor. & Ven. Dis.* **31**:304-313, 1947.
57. Stout, G. W. Reactivity of tests using cardiolipin antigens in limited number of nonsyphilitic cases. *Am. J. Syph., Gonor. & Ven. Dis.* **31**:314-321, 1947.
58. Becker, S. W. Practical aspects of verification tests for syphilis in office practice. *Am. J. Syph., Gonor. & Ven. Dis.* **31**:225-234, 1947.
59. Rein, C. R., and Kent, J. F. False positive tests for syphilis: study of their incidence in sporozoite-induced vivax malaria. *J. A. M. A.* **133**:1001-103, 1947.
60. Moore, J. E. *Penicillin in Syphilis.* 319 pp. Springfield, Illinois: Charles C Thomas, 1947.
61. Levaditi, C., and Vaisman, A. La pénicilline administrée par voie buccale, préserve-t-elle contre l'infection syphilitique expérimentale? *Bull. Acad. de méd., Paris* **130**:221-224, 1946.
62. Ross, S., Burke, F. G., and Olansky, S. Oral administration of penicillin: its use in one hundred and fifty cases. *New Eng. J. Med.* **236**:817-820, 1947.
63. Stokes, J. H. Recent advances in syphilogic diagnosis and treatment: nonspecific positive serologic test and use of penicillin. *Pennsylvania M. J.* **50**:718-725, 1947.
64. Heller, J. R., Jr. Results of rapid treatment of early syphilis. *J. Ven. Dis. Inform.* **27**:217-225, 1946.
65. Callaway, J. L., Noojin, R. O., Kuhn, B. H., Riley, K. A., and Flower, A. H., Jr. Treatment of early syphilis with penicillin. *South. M. J.* **39**:718-726, 1946.
66. O'Leary, P., and Kierland, R. R. Today's treatment of syphilis. *J. A. M. A.* **132**:430-434, 1946.
67. Sternberg, T. H., and Leifer, W. Treatment of early syphilis with penicillin. *J. A. M. A.* **133**:1-5, 1947.
68. News and Comment. Revised treatment schedules for syphilis. *Bull. U. S. Army M. Dept.* **5**:611, 1946.
69. Special Article. Management of syphilis. *J. A. M. A.* **134**:1535-1540, 1947.
70. Hill, W. R. Problems arising in treatment of syphilis with penicillin. *New Eng. J. Med.* **235**:919-924, 1946.
71. Cole, H. N., et al. Relapse during penicillin therapy of syphilis. *Ohio State M. J.* **42**:595-598, 1946.
72. Schwemlein, G. X. Treatment of syphilis with penicillin. *M. Clin. North America* **30**:649-658, 1946.
73. Frankland, A. W. Delayed appearance of syphilitic chancre after penicillin. *Brit. M. J.* **2**:159, 1946.
74. Dennie, C. C., and Dwyer, F. X. Syphilis: general considerations and method of treatment. *J. Kansas M. Soc.* **48**:1-12, 1947.
75. Kulchar, G. V., and Windholz, F. Clinical, radiologic, and pathologic aspects of late pulmonary syphilis — effects of penicillin therapy. *Am. J. Syph., Gonor. & Ven. Dis.* **31**:166-177, 1947.
76. Delbert, A. V., and Bruyere, M. C. Untreated syphilis in male Negro. III. Evidence of cardiovascular abnormalities and other forms of morbidity. *J. Ven. Dis. Inform.* **27**:301-314, 1946.
77. Russek, H. I., Cutler, J. C., Fromer, S. A., and Zohman, B. L. Treatment of cardiovascular syphilis with penicillin. *Ann. Int. Med.* **25**:957-959, 1946.

78. Sprague, H. B. Effects of malaria on heart. *Am. Heart J.* 31:426-430, 1946.
79. Tucker, H. A., and Dexter, D. D. Treatment of gummatous hepatic syphilis with penicillin: report of two cases. *Arch. Int. Med.* 78: 313-322, 1946.
80. Thomas, E. W., and Schur, M. Clinical nephropathies in early syphilis. *Arch. Int. Med.* 78:679-686, 1946.
81. Romansky, M. J., and Rittmann, G. E. Penicillin blood levels for twenty-four hours following a single intramuscular injection of calcium penicillin in beeswax and peanut oil. *New Eng. J. Med.* 233:577-582, 1945.
82. Romansky, M. J. Current status of calcium penicillin in beeswax and peanut oil: data from study of 600 cases and clinical observation of 4,000 patients given 60,000 injections. *Am. J. Med.* 1:395-411, 1946.
83. Romansky, M. J., and Rein, C. R. Treatment of early syphilis with calcium penicillin-oil-beeswax. *J. A. M. A.* 132:847-851, 1946.
84. Reynolds, F. W., and Moore, J. E. Syphilis: review of recent literature. *Arch. Int. Med.* 78:731-769, 1946.
85. Thomas, E. W., Landy, S., and Cooper, C. Rapid treatment of early syphilis with penicillin in beeswax and oil. *J. Ven. Dis. Inform.* 28:19-23, 1947.
86. Hirth, H. L., Dowling, H. F., Vivino, J. J., and Rotman-Kavka, G. Penicillin in beeswax and peanut oil, new preparation which is fluid at room temperature: absorption and therapeutic use. *J. Lab. & Clin. Med.* 32:34-41, 1947.
87. Hazel, O. G. Considerations with respect to application in private practice of penicillin therapy for early syphilis. *J. Ven. Dis. Inform.* 28:103-107, 1947.
88. Olansky, S., and McCormick, G. Syphilitic nephrosis: report of two cases. *J. Ven. Dis. Inform.* 28:45, 1947.
89. Pillsbury, D. M., and Loveman, A. B. Six- to twelve-month follow-up results in early syphilis treated by twenty-day intensive arsenobismuth system. *Am. J. Syph., Gonor. & Ven. Dis.* 31:115-123, 1947.
90. Sternberg, T. H., and Leifer, W. Treatment of early syphilis by twenty-six-week mapharsen-bismuth schedule. *Am. J. Syph., Gonor. & Ven. Dis.* 31:124-134, 1947.
91. Beerman, H., and Wammock, V. S. Dichlorophenarsine hydrochloride in treatment of syphilis. *Am. J. Syph., Gonor. & Ven. Dis.* 31: 150-162, 1947.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 34041

PRESENTATION OF CASE

A seventy-three-year-old man entered the hospital because of epigastric pain.

Ten and a half months before admission he began to have reddish spots and increased pigmentation of the legs associated with ankle edema. He finally visited the Out Patient Department three months before admission, and examination revealed stasis dermatitis, varicosities and purpura of the legs. There was a systolic murmur in the third left interspace. The urine gave a ++ test for albumin and showed gross hematuria and many granular casts. He was treated with ascorbic acid and boric acid soaks, which improved the stasis dermatitis but the purpura persisted, and he began to have occasional nosebleeds. Four weeks before entry he developed rather severe, continuous, nonradiating, epigastric pain, which was made worse by food and was associated with vomiting; there was no abdominal distention. He restricted his diet and lost weight (30 pounds in four weeks). The nosebleeds became more frequent; he noticed dark stools and blood in the urine. He became progressively weaker and finally had hiccoughs and repeated episodes of hematemesis.

The past history was indefinite. He had nocturia (twice a night) for years, had "always" had loose stools and may have had typhoid fever. He was a heavy drinker.

Physical examination revealed a poorly nourished, dehydrated, disoriented, dyspneic man. The positive findings included a purpuric rash on the upper and lower limbs, bleeding mucous membranes, some enlargement of the heart to the left, with an apical systolic, Grade II murmur radiating to the axilla and a rough systolic aortic Grade II murmur radiating to the neck, basal pulmonary rales, epigastric tenderness, a questionably palpable spleen, an enlarged prostate and slight ankle edema.

The temperature was 99°F., the pulse 85, and the respirations 24. The blood pressure was 132 systolic, 60 diastolic.

Examination of the blood disclosed a red-cell count of 3,200,000, with a hemoglobin of 8 gm., and a white-cell count of 6800, increasing to 13,000, with 93 per cent neutrophils. The urine had a specific gravity of 1.012 and gave a ++++ test for albumin and a + test for acetone; the sediment contained innumerable red cells. The prothrombin time was 28 seconds (normal, 19 seconds). The total protein was 6.92 gm. per 100 cc., with 2.78 gm. of albumin and 4.14 gm. of globulin, the nonprotein nitrogen was 185 mg. per 100 cc., and the carbon dioxide 8.9 milliequiv. per liter, increasing to 9.8 milliequiv. The serum calcium was 6.4 mg. and the phosphorus 11.0 mg. per 100 cc. A guaiac test on the stool was negative.

An x-ray film of the chest showed a few small areas of increased density above each leaf of the diaphragm. The heart was enlarged. A plain film of the abdomen showed enlargement of the lower pole of the left kidney.

The patient was given 300 cc. of blood. The pulmonary edema increased, and intravenous medication was stopped. The cyanosis and dyspnea increased. Tourniquets were applied to the limbs, and he was placed in an oxygen tent, with some relief. He was put on a low-phosphorus diet and given calcium gluconate, calcium levulinate, Amphojel, vitamin D and Berocca. Digitalization and tying of the leg veins were considered. The temperature mounted to 102°F., the pulse to 120, and the respirations to 130. On the third day the patient was found dead by the nurse, after having been fairly comfortable half an hour previously.

DIFFERENTIAL DIAGNOSIS

DR. WILLIAM BECKMAN: I might say that I am thoroughly bewildered by this case, but one thing seems clear: the patient had renal disease. The urinary findings, along with the elevated serum nonprotein nitrogen, the extremely elevated serum

phosphorus and definite acidosis as evidenced by a serum carbon dioxide content of only 8.9 milliequiv. per liter, make it impossible to entertain any other diagnosis than some kind of renal failure. One thing against the hypothesis of renal failure, it seems to me, is the normal blood pressure, which does not usually occur in this condition. This may have been due to shock at the time of admission or perhaps to the fact that the patient was in congestive heart failure. He did have some sort of heart disease; there was definite enlargement on physical and x-ray examination. There was an aortic systolic murmur radiating into the neck, which I think requires one to make a diagnosis of some degree of aortic stenosis, which according to many pathologists would mean rheumatic heart disease. But I do not believe that that view is held by the Department of Pathology in this hospital. In any event, I think that the patient had aortic stenosis. Further evidence of heart disease is provided by the presence of pulmonary edema, which certainly could have been the result of congestive heart failure, which in turn might have led to lowering of the blood pressure. Of course, the patient could have had pulmonary edema on the basis of renal disease alone. Scott, Schatzki and Bauer* reported a series of such cases some years ago. However, the definite evidence of heart disease, in the form of the aortic systolic murmur and the increase in the size of the heart, makes it more probable that the pulmonary edema was due to congestion.

A skin rash seems to have been the first symptom of this illness, but the description does not give an exact picture of it. It makes a great deal of difference, because I find it difficult to visualize skin diseases from a written description. I should like to know more about the rash. Were the lesions petechial in nature?

DR. BENJAMIN CASTLEMAN: They varied in size up to 1 cm. in diameter.

DR. BECKMAN: They seem to have been petechial rather than areas of purpura. That information helps. The thing that brought the patient to the hospital was pain in the stomach and the vomiting of blood. I am sure that people with uremia frequently complain of severe abdominal pain, and people with purpura vomit blood. He had had nosebleeds, however, so that he might have swallowed the blood and vomited it up again; we have no way of knowing. I cannot find any way of postulating or ruling out a lesion of the gastrointestinal tract itself. The most common one to cause hematemesis is peptic ulcer, but the description of the pain is just the opposite of what one would expect in ulcer because it was accentuated rather than diminished by the taking of food.

As I put the case together, the first syndrome that to my mind seemed to include most of the signs and symptoms was anaphylactoid purpura — Osler's disease. I have seen 2 patients with that syndrome, or at least I can remember the names of 2. As preparation for this discussion I examined their records, but they did not seem to be very much like this case. Both patients had had marked joint pains. The patient in the case under discussion had no joint symptoms whatever. I do not know the pathology of anaphylactoid purpura. One of the patients that I remember did not have an autopsy. The other one did — it was performed elsewhere, and we have not seen the slides. Therefore, even if that were the diagnosis, I would not know what pathology to expect. In Dr. Christian's textbook such patients are said to have the pathology of acute glomerulonephritis.

Yesterday afternoon I discussed the case with a fourth-year student, Mr. William Christianson, who suggested that the patient had had subacute bacterial endocarditis. At first I thought that this was an absurd hypothesis but then began to inspect the protocol more carefully. There are, indeed, many things in the protocol that do not necessarily support the diagnosis of subacute bacterial endocarditis over that of anaphylactoid purpura. In the first place, fever occurs in anaphylactoid purpura. The white-cell count was 13,000, with 93 per cent neutrophils, which is very suggestive of infection. The 2 cases of anaphylactoid purpura that I looked up had high white-cell counts but no marked increase in neutrophils. I am not sure that a skin rash is a necessary part of anaphylactoid purpura, but both my patients had a rash.

In short, in both conditions, fever, leukocytosis and skin rash are present. However, joint pain, apparently a characteristic feature of anaphylactoid purpura, was not present in this case. Likewise, heart-valve disease, on which subacute bacterial endocarditis always develops, was present in this case. Apparently, an aortic systolic murmur was heard when he was examined in the Out Patient Department three months before admission; it was to the left of the sternum. When he came in, an aortic systolic murmur in the aortic area, transmitted to the neck, was heard. Changes in murmurs are a feature of subacute bacterial endocarditis, as is the gross hematuria due to renal infarcts. The patient had a questionably palpable spleen, which is also considered to be due to splenic infarction in this disease. Yesterday evening I did not believe that I had ever encountered a patient with embolic nephritis to such a degree as this. In the summer of 1937, we had a man on the wards whose difficulty was marked hematuria with uremia. We thought that he had chronic nephritis, but at autopsy it was discovered that he had subacute bacterial endocarditis with embolic nephritis of a similar degree, with uremia. I am therefore going to "stick my neck out" and say that this man had subacute bacterial endocarditis with embolic nephritis, congestive heart failure on the basis of arteriosclerotic heart disease, aortic stenosis and pulmonary edema,

*Scott, T., Schatzki, R., and Bauer, W. Pulmonary edema: its roentgenologic appearance in acute glomerulonephritis without signs of cardiac failure. *J. A. M. A.* 114:613, 1940.

perhaps as a result of the combination of uremia and congestive heart failure. I have not seen the x-ray films yet, but I am not going to change my diagnosis.

DR. STANLEY M. WYMAN: Most of the enlargement of the heart is in the left chamber. The definite areas of density described in the lower lung field are probably atelectasis in both bases.

DR. ISAAC TAYLOR: Is there any pulmonary edema?

DR. WYMAN: I cannot see any. The question of the mass in the left kidney I cannot quite corroborate. I believe that the spleen is enlarged.

DR. BECKMAN: The kidneys were said to be big, and such enlargement is compatible with embolic nephritis, although I cannot rule out pyelonephritis.

DR. CASTLEMAN: Have you any comment, Dr. Scott?

DR. THORNTON A. SCOTT: I agree that the patient may have had a calcific aortic valve, with superimposed bacterial endocarditis.

DR. SEDGWICK MEAD: Were there any splenic infarcts? They are often associated with abdominal pain.

DR. BECKMAN: And cerebral infarcts — to account for the mental confusion.

CLINICAL DIAGNOSES

Chronic glomerulonephritis, with uremia.
Arteriosclerotic heart disease.

DR. BECKMAN'S DIAGNOSES

Subacute bacterial endocarditis, aortic valve.
Embolic nephritis.
Arteriosclerotic heart disease, with congestive failure.
Aortic stenosis.
Pulmonary edema.

ANATOMICAL DIAGNOSES

Subacute bacterial endocarditis, aortic valve.
Subacute glomerulonephritis.
Embolic nephritis.
Renal and splenic infarcts.
Papillary adenoma of left kidney, with necrosis and hemorrhage.
Calcareous aortic stenosis.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Autopsy confirmed the diagnosis of subacute bacterial endocarditis located on a previously calcific aortic valve. There was moderate interadherence of the aortic cusps, with deposits of calcium there — not the full-blown calcareous stenosis that produces a systolic thrill but enough stenosis to produce a murmur. Implanted on this old process were numerous vegetations, 3 to 6 mm. in diameter, a smear of which at the time of autopsy showed streptococci.

The spleen weighed over 400 gm. and contained many small infarcts. There were also a few emboli to the kidneys, but the few small renal infarcts were certainly not enough to produce uremia. Occasionally, in cases of subacute bacterial endocarditis, especially in those with uremia, not only embolic nephritis but also a true glomerulonephritis occurs, which is what this patient had. Many of the glomeruli showed the crescent formation characteristic of glomerulonephritis. There was still another renal lesion. In the left kidney was a large mass, 10 cm. in diameter, which at autopsy looked like renal-cell carcinoma. It was very necrotic and full of purulent material, and microscopical sections showed a benign papillary renal adenoma. This may have been a precursor of renal-cell carcinoma, but at autopsy there was no evidence of cancer. I am almost certain that the gross hematuria that this patient had probably came from the renal adenoma rather than from the infarcts or the nephritis.

There was not much edema of the lungs. There was some congestion and some hemorrhage into the alveoli, which one not infrequently sees in uremia. The purpura was probably a combination of the uremia and the bacterial endocarditis. I am not sure that the lesions were true petechiae.

DR. WARREN BENNETT: As I recall them, I think that they were more like purpura.

DR. TAYLOR: That was our impression.

A PHYSICIAN: Was the liver normal? Was there any evidence of central congestion or cirrhosis? And how about the gastrointestinal tract?

DR. CASTLEMAN: The liver was normal. There was only an acute erosion in the stomach. I believe that the epigastric pain was probably due to the infection and to hemorrhage within the renal adenoma.

DR. J. W. ZELLER: What did the parathyroid glands show?

DR. CASTLEMAN: They were normal.

A PHYSICIAN: Did the post-mortem cultures show anything?

DR. CASTLEMAN: No.

CASE 34042

PRESENTATION OF CASE

A thirty-two-year-old housewife entered the hospital because of vaginal bleeding of ten months' duration.

She had always been in good health. The menses had begun at the age of ten and a half, with regular periods every twenty-eight days, lasting three to five days. She was delivered uneventfully of her first child at the age of twenty-six. Twenty months before admission she became pregnant for a second time. Between the third and fourth months she had a two-week episode of vaginal bleeding and was confined to bed. The pregnancy continued without further difficulty to a normal delivery. Following delivery she had four bleeding episodes, two of which required curettage and several transfusions. The tissue removed was said to be normal. The

last episode began two weeks before entry and continued with the passage of large clots to the day of admission. There was no pain. No tissue was recognized among the blood clots.

Physical examination was entirely negative, except for slight pallor of the mucous membranes.

The temperature, pulse and respirations were normal; the blood pressure was 120 systolic, 76 diastolic.

Urinalysis revealed a specific gravity of 1.018, a ++ test for albumin and a 0 test for sugar. The hemoglobin was 13.2 gm. The prothrombin time and bleeding and clotting times were normal.

On the third hospital day an operation was performed.

Differential Diagnosis

Dr. Somers Sturgis: We have the history of a completely normal ovulatory function. The patient was delivered of her first child at the age of twenty-six. Twenty months before admission she became pregnant for the second time. Between the third and fourth months she had a two-week episode of vaginal bleeding and was confined to bed. The pregnancy continued without further difficulty to a normal delivery. She may have had a low implantation of the placenta or something of that sort, which was not, however, significant enough to interrupt the pregnancy since a normal delivery followed, and therefore the cause of the bleeding in the third and fourth months probably had little to do with the present chief complaint — the vaginal bleeding that started a month after delivery and ten months before entry. Following delivery — that is, in the last ten months — she had four bleeding episodes, two of which required curettage and several transfusions. That means that she had rather extensive bleeding. The tissue removed was said to be negative — negative for tumor, I assume. The last episode began two weeks before entry and continued with the passage of blood clots to the day of admission. I do not believe that the large clots had any particular significance. Recent work on the menstrual discharge shows that menstrual blood does generally clot inside the uterus and that the clot then becomes digested through enzymatic or fibrinolytic action, and for this reason, menstrual discharge does not generally clot because it has already clotted. If there are large clots it seems to be significant merely of more than usually profuse bleeding so that the clot does not stay in the uterus long enough to be digested. There was no pain. No tissue was recognized among the blood clots. Of course, fetal tissue could have been missed.

Physical examination on admission was entirely negative, except for slight pallor of the mucous membranes. I assume that to mean that examination of the pelvis was negative too. The temperature, pulse and respirations were normal. The blood pressure was normal. The urine was essentially normal, with a small amount of albumin. The hemoglobin was 13.2 gm. The patient had had enough bleeding to have had two dilatations and curettages and several transfusions, and she had been bleeding, with large clots, for two weeks on entry. Yet she came in with a hemoglobin of 13.2 gm., which I should think indicates that she had had rather good supportive measures in the way of iron in the meantime. The prothrombin, bleeding and clotting times were normal. On the third day an operation was performed.

Essentially this is the story of a thirty-two-year-old para II with a completely normal past history and 2 normal children; the only thing of significance that I can find at all in this story is the fact that there was a great deal of bleeding originating after the second delivery. Other than this I cannot see that there is anything at all to point to any diagnosis, and one is forced to consider all the causes of uterine bleeding in a thirty-two-year-old multipara. I think that one could summarize the causes as obstetric and systemic and those due to benign and malignant tumors.

Because the bleeding originated after delivery, one might consider the obstetric possibilities first. Chorioepithelioma causing post-partum bleeding cannot be excluded. We do not know precisely when the episodes of bleeding occurred in the last ten months. In other words we cannot tell whether she had another pregnancy and a miscarriage, or perhaps a missed abortion, or whether, in spite of the fact that no tissue had been found and the dilatations and curettages were negative, a chorioepithelioma developed from such a miscarriage. I do not believe that we can get any further information on that point and must consider it as a possibility. Again, she may have had a placental polyp from another such miscarriage that could have been missed in two dilatations and curettages. She may have had puerperal sepsis causing pelvic inflammatory disease, which interfered with the function of the ovaries and the regularity of the periods, but I think that one could throw that out on the basis of the negative pelvic examination.

In considering systemic causes, anemia itself certainly was not a factor. There is no indication of hypothyroidism or other systemic disease in this history. Could this amount of bleeding have occurred from disorganization of the endocrine system following delivery? Of course, hyperplasia of the endometrium and episodes of long profuse bleeding are frequent while the patient is establishing her rhythm again following delivery. That might give a "negative" dilatation and curettage and can cause fairly profuse hemorrhage. Again, it is hard from what we are given to rule that out.

Of the benign tumors one thinks first of fibroid. If the pelvic examination was negative, there was not much enlargement of the fundus. Could the patient have had a small submucous fibroid that was involved in the two-week episode of bleeding during the second pregnancy and yet was too small

to be felt on pelvic examination? I rather think that the chances are against that possibility, because if a submucous fibroid caused two weeks' bleeding during a pregnancy I should think that it would have been responsible for an abortion of that particular pregnancy. Certainly, the patient did not have a large fibroid or it would have been discovered at curettage. She may have had a benign polyp in the endometrium, and this again could conceivably have been missed by two dilatations and curettages, but it does not seem likely. She may also have had adenomyosis of the uterus, even though the regularity and normality of this history before the present episode seem to discount such a possibility.

Could she have had endometrial cancer? I wonder if a vaginal smear was taken. Of course, if it was negative it would tend to make one think that this was not endometrial cancer, although in our laboratory we have missed the diagnosis in about 20 per cent of the group of cancers of the fundus on vaginal smear. The patient presumably did not have cancer of the cervix, which would have been discovered on pelvic examination.

Briefly, these are some of the common causes of uterine bleeding, and the history does not leave us with very much to go on. I should like to ask if it is known whether the patient had stilbestrol at any time in the period of two weeks' bleeding when she was put to bed during the second known pregnancy. A number of patients have been given massive doses of stilbestrol for threatened miscarriage. I have heard of 2 that had hyperplasia of the endometrium and intensive flowing following normal delivery after stilbestrol treatment during pregnancy. If this patient did not have stilbestrol I am really at a loss to know what to guess as the cause in this case. I am inclined to guess that there might have been a placental polyp or a retained placental fragment due to a miscarriage of a third pregnancy following the second delivery.

DR. TRACY B. MALLORY: Have you any suggestion, Dr. Smith?

DR. JUDSON SMITH: Can you date the episodes of bleeding more accurately?

DR. JOE V. MEIGS: The patient bled during the last two weeks before admission.

DR. SMITH: Yes; but what was the relation to her delivery?

DR. MEIGS: Ten months after the delivery.

DR. SMITH: It was too late for the patient to have retained products of conception. If she had a placental polyp she should have started bleeding long before, and if anybody with any competence did two dilatations and curettages on her he should have got the polyp out. It is a perfectly good history for a chorioepithelioma, and the most important fact has not come out at all and that is whether an Aschheim–Zondek test was performed and whether or not it was positive.

DR. MEIGS: The test was not done.

DR. SMITH: There have been patients with negative Aschheim–Zondek tests and negative curettage that turned out to have chorioepithelioma. But that is a little bit fantastic.

CLINICAL DIAGNOSES

Hyperplastic endometrium.
Anovulatory menstruation.

DR. STURGIS'S DIAGNOSIS

Placental polyp.

ANATOMICAL DIAGNOSIS

Normal uterus.

PATHOLOGICAL DISCUSSION

DR. MALLORY: Dr. Meigs, do you want to tell us what you found?

DR. MEIGS: This patient just bled, that is all. She kept bleeding even though there was absolutely nothing wrong that we could make out. Since she had cervical lacerations and a moderate amount of prolapse the best way to treat her was to do a reconstructive procedure with removal of the uterus.

DR. MALLORY: The uterus was perfectly normal. The endometrium was in a proliferative phase. It was not even significantly hyperplastic, so that we have no anatomic explanation of the bleeding.

DR. SMITH: I have seen 2 or 3 cases of persistent bleeding after a pregnancy in which no cause was ever found and the only cure was a hysterectomy.

DR. MEIGS: The patient bled herself down so that she was miserable, and then somebody curetted her, and then the same thing started over again. She had been bleeding for two weeks and was much upset about it, and operation was the only way to stop the bleeding. I think that she was the kind of patient one sometimes wants to give radium to.

If we read over the case histories on gynecologic rounds in the hospital there is no question that there are many patients who come in with unexplained bleeding; why they bleed, I do not know. Perhaps women ought not to menstruate so often as they do. As soon as a woman comes of age and delivers an egg she is biologically supposed to become pregnant like any animal, and she is supposed to keep pregnant and nurse, and keep pregnant and nurse, until she either cannot have any more children physiologically or she dies. I think that we are bound to have, and that we do have a great many cases of unexplained bleeding. Perhaps we shall never know the answer.

DR. MALLORY: Our policy in these exercises is ordinarily to discuss cases in which an anatomic specimen establishes the diagnosis beyond reasonable doubt. It is well worth while occasionally to remind ourselves that the most careful histologic examination may reveal nothing in the face of severe functional disorders.

The New England
Journal of Medicine
Formerly
The Boston Medical and Surgical Journal
Established 1828

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY
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SUBSCRIPTION TERMS: $7.00 per year in advance, postage paid, for the United States (medical students, $4.00 per year); Canada, $8.00 per year (Boston funds); $9.50 per year for all foreign countries belonging to the Postal Union.

MATERIAL should be received not later than noon on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

POSTGRADUATE LECTURE COURSE — 1948

THE third annual postgraduate lecture course in general medicine, presented by the Massachusetts Medical Society and arranged by the Committee on Postgraduate Education, will be held again this year in Sanders Theater, Harvard University, Cambridge. Beginning on Monday, March 8, at 6:00 p.m., the course will run regularly on Mondays from 6:00 to 9:00 and on Wednesdays from 3:00 to 6:00 through May 5. The course is free to all physicians residing in New England; membership in the Massachusetts Medical Society is not necessary for attendance.

Special features presented for the first time this year will be sessions on cancer diagnosis and treatment — the first two of the course — presided over by Dr. Charles C. Lund and Dr. Ira T. Nathanson; a session on April 26 on convulsive seizures, presented by Dr. Wilder Penfield, of Montreal, and Dr. H. Houston Merritt, of New York City, under the joint chairmanship of Dr. William G. Lennox and Dr. Maxwell E. Macdonald; and a clinical, roentgenologic and pathological session to be presided over by Dr. Merrill C. Sosman on April 12. An outline of the program appears on page xi in this issue of the *Journal*.

This lecture course, an outgrowth of the work of the Committee on Postwar Planning, has met with a universal response. In 1947 over 1200 physicians registered for forty-eight hours of instruction; as President O'Hara pointed out in his address to the Society in May, 1947, the course was the equivalent in hours of instruction of a complete college education for over twenty students. Dr. W. Richard Ohler, chairman of the Committee on Postgraduate Education, was referred to as "president of Sanders College," and Dr. Lewis M. Hurxthal, chairman of the subcommittee in charge of the course, as "dean."

Even greater success is expected for the coming course. As before, return postal cards will be sent to all registered physicians in Massachusetts. Those who wish to register immediately for the course should do so by writing to the Postgraduate Lecture Course Committee, Massachusetts Medical Society, 8 Fenway, Boston.

MEDICAL CARE FOR VETERANS

IN THE October 11 issue of the *Journal of the American Medical Association* appears a most encouraging report from the National Medical Advisory Board of the American Legion. This board submitted several recommendations, which were adopted by the National Convention of the American Legion at its meeting in New York in August, 1947. In general, it appears that the American Legion is enthusiastic about the improved care given to veterans, particularly in hospitals that are now affiliated with medical schools through the deans' committees. The Legion went on record as favoring medical research in all its

phases, and approved of the residency program. It even recommended the extension of this residency program to include outpatient clinics, in the expressed belief that this approach would assure the veteran the best medical care possible.

Those who are familiar with the problem consider the extension of the resident teaching service to the outpatient clinics a vital necessity, and it is encouraging to have a group of lay people recommend the adoption of this plan. In addition, the Legion recommends that an intern service in the hospitals where it is appropriate be adopted, and it is in favor of introducing clinical clerkships in the clinical hospitals, to be under the direction of the resident staff members and the supervision of the deans' committees.

This is another step forward. If these recommendations were adopted, there would be available in Greater Boston a vast amount of material that is not now utilized for teaching, and the use of interns and clinical clerks would do much to lighten the routine of the residents now in training. This would result in even better use of these residents for the actual care of the patient. The Legion concluded its recommendations as follows: "It is recommended to the Congress of the United States that when economy is to be practiced in the nation, it should not be at the expense of the health of the veterans who saved the nation."

The policies of General Bradley and General Hawley established good principles for the care of the disabled veteran and, in the past two years, have produced extraordinarily gratifying results, particularly as they apply to the affiliated hospitals with their resident training programs. It is even more gratifying to learn that these policies and their results have so impressed the committee of the American Legion that the Legion has gone on record as stated above. This is no time to be complacent, however. The good results of these policies will continue only so long as they are in charge of public-spirited and unselfish personnel. The care of war casualties must be maintained on a high level and with the minimum amount of interference from those whose policies might be unduly swayed by political expediency.

A. D. A. FORECAST

The American Diabetes Association on January 1, 1948, put into publication a new, small journal for the general public. The *A. D. A. Forecast* "is designed to extend the doctor's influence, to save his time and to aid in the control of diabetes and the detection of cases yet undiagnosed."

The annual subscription rate for residents of the United States and Canada is $2.00 for twelve issues. Subscription blanks may be obtained from doctors and druggists and from the American Diabetes Association, Inc., 1 Nevins Street, Brooklyn 17, New York.

Even with the probability that too much printed matter, in the aggregate, sees the light of day, there is always room for more that conveys a message. This is the case with the *A. D. A. Forecast*, which we welcome for the value it will have to diabetic patients the country over.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

BRIGHT — James C. Bright, M.D., of Fall River, died on November 12. He was in his seventy-fifth year.

Dr. Bright received his degree from Jefferson Medical College of Philadelphia in 1907.

His widow survives.

COPELAND — Elmer H. Copeland, M.D., of Northampton, died on December 25. He was in his eighty-seventh year.

Dr. Copeland received his degree from New York Homeopathic Medical College and Flower Hospital in 1893. He was a member of the staff of the Cooley Dickinson Hospital and was formerly a censor, commissioner of trials and vice-president of the Hampshire District Medical Society.

Two daughters, two sons and two grandchildren survive.

KING — George C. King, M.D., of Fall River, died on December 21. He was in his sixty-second year.

Dr. King received his degree from Tufts College Medical School in 1909. He was a member of the American Academy of Pediatrics and the New England Pediatric Society and was a fellow of the American Medical Association. He was a member of the Board of Trustees, chief pediatrician and member of the staff of the Truesdale Hospital, as well as a former president of the Fall River Anti-Tuberculosis Society.

His widow, a daughter, three sons, his mother, three brothers, two sisters and two grandchildren survive.

LORD — William J. Lord, M.D., of Great Barrington, died on December 16. He was in his forty-first year.

Dr. Lord received his degree from Albany Medical College in 1939. He was an officer in the United States Army Medical Corps in World War II.

His widow, his mother, a daughter and two sons survive.

REESE — John A. Reese, M.D., of Attleboro, died on December 10. He was in his sixty-third year.

Dr. Reese received his degree from Tufts College Medical School in 1908. He was chief surgeon of Sturdy Memorial Hospital and was a fellow of the American College of Surgeons and American Medical Association.

His widow, a son and a daughter survive.

MISCELLANY

FIFTH ANNUAL TROPICAL MEDICINE AWARD

The fifth annual award of the Richard P. Strong Medal for outstanding service in the field of tropical medicine was made to Dr. Neil P. Macphail, veteran surgeon and sanitarian of the United Fruit Company at Quirigua, Guatemala, it was recently announced. The award was presented at the annual dinner of the American Foundation for Tropical Medicine at the Waldorf Astoria in New York City on January 8.

Dr. Macphail has been active in tropical medicine in Central America since 1907, when he accepted a position as quarantine doctor for the plague-ridden port of Belize, British Honduras. In the following year he became medical superintendent of the United Fruit Company's East Coast division of Guatemala, a position he still holds. During the past forty years, his efforts in combating yellow fever, cholera, endemic malaria, dysenteries, snake bite, night blindness and other tropical maladies have earned for him the nickname "El Amado Medico" (the beloved doctor).

Other recipients of the medal, in addition to Dr. Strong, have been Rear Admiral Edward R. Stitt, United States Navy, internationally noted author of basic texts on tropical medicine; Brigadier General George R. Callender, United States Army, a leader on tropical medical administration during World War II; and Dr. Neil H. Fairley, Australian authority on tropical diseases.

AGING OF TWINS

Columbia University has been awarded a grant of $31,500 by the Rockefeller Foundation for the "investigation of the interaction of hereditary and environmental factors in relation to problems of aging." The grant is a renewal of an original gift made by the Foundation in 1945 to the New York State Psychiatric Institute, a part of the Columbia-Presbyterian Medical Center.

In the study, the health status and activities of New York State twins over sixty years of age who reside in institutions for the aged are being compared with those of twins outside institutions.

CORRESPONDENCE

ANOTHER DISTINGUISHED WOMAN PHYSICIAN

To the Editor: I was very much interested in reading the editorial "Madame President" in the November 13 issue of the *Journal.*

May I suggest that, in addition to laying claim with "pride and distinction" to being the home of the first woman president of the American Public Health Association, Dr. Martha May Eliot, your great medical center can also lay claim with "pride and distinction" to being the home of the first woman president of the American Gastroenterological Association, Dr. Sara M. Jordan, chief of the Division of Gastroenterology of the Lahey Clinic.

Dr. Jordan was for many years the only woman member of the American Gastroenterological Association, and two years ago was elected its first woman president. She furthermore enjoys the distinction of being one of the nation's outstanding woman clinicians, being especially well recognized for her very creditable work in the field of gastroenterology.

RUSSELL S. BOLES, M.D.

Rittenhouse-Plaza, Philadelphia

CLINIC CONSULTATION SERVICE AT JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

To the Editor: We should like to call your attention to the fact that, owing to enlarged facilities, we can now take ambulatory diagnostic patients through our Clinic Consultation Service with a minimum of waiting. On our present appointment schedule a patient's first visit can be planned within a week.

This service is similar in every way to the diagnostic service rendered to patients admitted to the hospital, except that the patients are ambulatory and no benefits are paid for such care under the existing Massachusetts Blue Cross.

Because of the pressure for hospital beds we are anxious to care for patients on an ambulatory basis, and we should appreciate your co-operation in directing as many patients as possible to the ambulatory Clinic Consultation Service rather than having them admitted to the hospital.

Appointments for the Clinic Consultation Service can be made by calling HA 6-5650, Extension 377.

RICHARD T. VIGUERS, *Administrator*

Joseph H. Pratt Diagnostic Hospital
30 Bennet Street
Boston

BOOK REVIEWS

R K G Rheocardiography: A method of circulation's investigation and diagnosis of circular motion. From the Nerve-Clinic, the Physiological Institute, and the Pharmacological Institute of the University of Vienna. By W. Holzer, K. Polzer, and A. Marko. Translated by Mrs. Emma M. Kreidl. 8°, paper, 43 pp., with 44 illustrations. Vienna: Wilhelm Maudrich, 1946.

This small booklet, which was published in Vienna in 1945 and translated into crude English by Emma Kreidl in 1946, was issued as the first volume of a collection of books on the application of natural science in physics to medical research.

The rheocardiograph is a device for measuring electrical impedance. When it is connected to the right and left arms of a subject by means of electrocardiographic electrodes, a rhythmic motion that corresponds to the heart beat is registered. The authors claim that this rhythmic registration represents the action of the left ventricle. The rheocardiograms recorded in this booklet closely resemble arterial pulse tracings but lack their details.

Electrical-impedance measurement of the body is not new. Hubert Mann (*Proc. Soc. Exper. Biol. & Med.* 36:670, 1937) states:

> When the electrical conductivity of any part of the body is measured by means of an alternating current bridge it is found that this conductivity shows a rhythmic variation synchronous with the pulse. Neybour (Medical Physics, Glasser) describes the method with a complete bibliography and refers to the curve as an electrical plethysmogram.

Electrokymographic records of the left ventricle are dissimilar to the rheocardiogram. An electrokymogram of the aorta shows a greater similarity to the rheocardiogram, as does any large arteriogram.

It is worth while to explore the application of all kinds of new technics to medical science. Little of value has been shown by such application of rheocardiography as that presented in this book, but whether something more useful will eventually be demonstrated remains for the future to reveal.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

State Central Case Record Systems and Local Case Registers for Tuberculosis. 12°, cloth, 88 pp. Washington, D. C.: Federal Security Agency, United States Public Health Service, Tuberculosis Control Division, Washington, D. C., 1947.

To be fully effective, tuberculosis-control programs must be supported by accurate and complete record systems. This manual has been prepared for the purpose of assisting in establishing uniform state record systems and co-ordinating them with local case registers. The primary objectives of the state system are program management, supervision and evaluation. Local case registers are necessary for case

management and evaluation and definition of local problems. The material presented in this manual is based on extensive field studies, particulariy in the states of Kansas and Oregon. The text is divided into a number of sections devoted to the various details of equipping, setting-up and managing state record systems and local registers. The binding is done in the loose-leaf style, not adapted to rugged use. The printing and chart work are excellent. The manual should prove useful to public-health workers interested in tuberculosis work.

Medical Addenda: Related essays on medicine and the changing order. Studies of the New York Academy of Medicine Committee on Medicine and the Changing Order. 8°, cloth, 156 pp. New York: The Commonwealth Fund, 1947. $1.75.

This supplementary volume contains six essays by eminent authorities on special problems related to the general studies of the committee. Dr. James A. Miller writes on "The doctor himself," stressing the fact that the quality of medical service depends primarily on the physician himself. The late Dr. Louis Hamman discusses psychosomatic medicine. The remaining papers are by Miss Mary A. Cannon and Miss Harriett M. Bartlett on medical social work, Winifred W. Arrington on psychiatric social work, Dr. Howard A. Rusk on rehabilitation and convalescence and Dr. Ernst P. Boas on chronic diseases. The publication is excellent in all ways, and the volume should be in all medical and social libraries.

Health and Rehabilitation through Chest Training. By Samuel Delano, M.D. 8°, cloth, 142 pp., illustrated. New York: Williams-Frederick Press, 1947. $2.50.

In this small volume Dr. Delano explains his special system of chest training. The text is divided into three parts, one, physiology of the chest, lungs, diaphragm and breathing; two, special system of chest movements, with directions for their use; three, results of chest training in pathologic conditions. The text is well printed, with a good type on good paper and is well illustrated with good photographs and x-ray plates of the chest. The book should be in all collections on physical medicine.

NOTICES

MASSACHUSETTS PUBLIC HEALTH ASSOCIATION

The annual meeting of the Massachusetts Public Health Association will be held on Thursday, January 29, at the Massachusetts Institute of Technology. There will be section meetings at 3:30 p.m. A dinner meeting will be held at 6:00 p.m. in the Campus Room, Massachusetts Institute of Technology Graduate House; the charge will be $1.75, including tax and tip (reservations must be made by January 26 with Mrs. Elizabeth Caso, Harvard School of Public Health, 55 Shattuck Street, Boston). At the evening meeting at 7:00 p.m. C. Mayhew Derryberry, Ph.D., chief, Office of Health Education, United States Public Health Service, will speak on the subject "Health Education — a Catalyst."

NATIONAL CONFERENCE ON MEDICAL SERVICE

The National Conference on Medical Service will be held at the Palmer House, Chicago, on Sunday, February 8, the 1948 session being opened by the president of the Conference, Dr. Creighton Barker, of New Haven, Connecticut, at 9:30 a.m. "The Practice of Medicine by Hospitals, Health Departments and Medical Schools" will be discussed by Everett W. Jones, general manager of the *Modern Hospital*, Chicago, and Dr. Lowell S. Goin, of Los Angeles. Dr. L. F. Foster, of Bay City, Michigan, will speak on the topic "Medical Public Relations Begins in the Doctor's Office," and Dr. Thomas P. Murdock, of Meriden, Connecticut, and Janet Geister, of Chicago, on "Nursing Problems in America."

The afternoon will be devoted to panel presentations of the subjects, general practice and specialty boards, to be participated in by Dr. Wingate M. Johnson, of Winston-Salem, North Carolina, Dr. C. F. Wilkinson, of Ann Arbor, Michigan, Dr. Leroy E. Parkins, of Boston, Dr. Paul Titus, of Pittsburgh, and Dr. C. N. H. Long, of New Haven, Connecticut.

AMERICAN HOSPITAL ASSOCIATION

The American Hospital Association will hold the first in the 1948 series of institutes on hospital-personnel relations at the Henry Grady Hotel, Atlanta, Georgia, on February 23–25. This institute is planned to give assistance and to stimulate planning for improved employee relations, not to train personnel officers. Administrators, assistant administrators and personnel officers will be helped to develop and maintain efficient work forces.

Limited to an enrollment of 75, the institute is planned to utilize the three days fully, and those attending are urged to plan longer stays in Atlanta if they desire to visit local hospital or scenic spots.

NEW YORK TUBERCULOSIS AND HEALTH ASSOCIATION

The Annual Conference of the New York Tuberculosis and Health Association will be held on Tuesday, March 9, at the Hotel Pennsylvania, New York City. Authorities on tuberculosis, social hygiene and health education will present papers at morning and afternoon sessions. The luncheon meeting will feature an outstanding speaker.

The Tuberculosis Sanatorium Conference of Metropolitan New York will meet simultaneously and will elect officers for the coming year.

FIFTIETH ANNIVERSARY OF CORNELL UNIVERSITY MEDICAL COLLEGE

Cornell University Medical College celebrates its fiftieth anniversary this year. The Alumni Day, which will be held on March 11 at the College, is an event of special significance to all graduates. The program will include registration in the morning, with luncheon at the Nurses Residence, to be followed by a business meeting and a schedule of rounds and conferences in all departments. Dinner will be served at the Roosevelt Hotel, and dancing will conclude the day.

INTERNATIONAL COLLEGE OF SURGEONS

The sixth international assembly of the International College of Surgeons will be held in Rome, Italy, at the invitation of the Italian Government, during the week of May 16–23, under the presidency of Professors Raffaele Bastianelli and Raffaele Paolucci, of Rome, and Mario Dogliotti, of Turin. The secretary of the assembly is Professor Giuseppe Bendandi, of Rome. Detailed information may be obtained from Dr. Max Thorek, general secretary, 850 Irving Park Road, Chicago 13. For travel information, application should be made to the All Nations Travel Bureau, 38 S. Dearborn Street, Chicago, the official travel representatives for this assembly.

NEUROPSYCHIATRIC RESIDENCY AT VETERANS ADMINISTRATION HOSPITAL, LYONS, NEW JERSEY

Openings are available in neuropsychiatric residency at the Veterans Administration Hospital, Lyons, New Jersey.

The program consists of one, two or three years of training with intensive postgraduate teaching in clinical neurology and psychiatry, psychopathology, clinical psychology and related sciences and in neuroanatomy, neurophysiology, neuropathology and neuroroentgenology, as well as experience in female and child outpatient psychiatry and in-hospital training for female patients and feebleminded children and juvenile delinquents.

The type of instruction, supervision and training is carried out in accordance with the requirements of the American Board of Psychiatry and Neurology.

The residency has been approved by the Council on Medical Education and Hospitals, American Medical Association, and by the American Board of Psychiatry and Neurology.

(*Notices concluded on page xvii*)